KCE REPORT 343Cs

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SUMMARY

DO INNOVATIVE MEDICINES AGAINST CANCER ALWAYS HAVE A REAL ADDED VALUE?

KCE REPORT 343Cs
HEALTH TECHNOLOGY ASSESSMENT

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SUMMARY

DO INNOVATIVE MEDICINES AGAINST CANCER ALWAYS HAVE A REAL ADDED VALUE?

MATTIAS NEYT, CARL DEVOS, NANCY THIRY, GEERT SILVERSMIT, CINDY DE GENDT, NANCY VAN DAMME, DIEGO CASTANARES-ZAPATERO, NICOLAS FAIRON, FRANK HULSTAERT, LEEN VERLEYE

FOREWORD

Advances in medicine have brought many benefits, and the fact that new drugs regularly enter the market is therefore to be welcomed. It is also highly understandable that those suffering from serious conditions such as cancer want access to these new drugs as swiftly as possible.

Which is why Belgium and many other European countries permit deviation from the traditional reimbursement procedure in the case of promising new medicines, before their added value for the patient has been sufficiently proven. Indeed, provisional reimbursement can be awarded via so-called managed entry agreements (MEAs), in anticipation of additional scientific data.

It is, of course, crucial that the added value of such medicines is effectively demonstrated after a suitable period of time. After all, not all innovations are by definition an improvement. At the request of the NIHDI (National Institute for Health and Disability Insurance), the KCE (Belgian Health Care Knowledge Centre) investigated to what extent a selection of new cancer drugs that have been reimbursed in Belgium in recent years have provided genuine added value for the patient, and what budgets are associated with this. You can find the results of the investigation in this report.

During our study, we identified a significant number of methodological difficulties, which means that the study results are often insufficiently informative to determine the genuine added value for the patient. Coupled with the increasing use of MEAs, in which the actual prices paid remain confidential, this leads to an opaque system, the consequences of which are difficult to gauge. In 2019, the MEA budget already represented approximately one quarter of the total budget for medicines in Belgium.

It is now up to European and national governments to address the issues identified, and to determine how they develop in the future. We hope this report will provide an impetus for steps towards a transparent and sustainable reimbursement system for medicines that makes efficient use of public resources and provides patients and their doctors with sufficient guarantees of clear and reliable added value.

Christophe JANSSENS
Deputy General Director a.i.

Marijke EYSSEN
General Director a.i.

KEY MESSAGES

The KCE was asked to investigate to what extent a selection of innovative oncological drugs that were introduced in the last 15 years have provided added value for the Belgian population and whether the expenditure for this represented efficient use of the available resources. This synthesis provides an overview of our findings. We also present our recommendations at the end of the synthesis. Please refer to the scientific report for more details.

1. The European Medicines Agency (EMA) typically markets cancer drugs based on surrogate endpoints or single-arm trials, which do not always translate into the substantiated improved outcomes that matter most to patients, i.e. survival and quality of life. The literature reveals that, even after they have entered the market, a significant degree of uncertainty remains for the majority of oncological drugs with regard to their added value for the patient or it turns out that this added value was limited. Coupled with the high prices charged, these uncertainties put policy makers in a difficult position when deciding which treatments should be reimbursed, all the more so as patients' expectations are high. The approval and reimbursement of expensive drugs with little or no benefit leads to inefficient use of the limited resources available and undermines the affordability and quality of our healthcare system.
2. Data from the *Belgian Cancer Registry* (BCR) on approximately 891 000 tumours from approximately 814 000 patients (diagnosed between 2004-2017) was made available for the purposes of this study. This data was linked to reimbursement data from the Inter-Mutualistic Agency (IMA) for the purposes of mapping expenditure on oncological drugs. The patient survival data was obtained from the Crossroads Bank for Social Security. These different types of observational data were mapped for 12 types of cancer.
3. 40 different types of innovative oncology drugs were selected from these 12 indications, with further information on efficacy and cost-effectiveness then compiled on them. Given the large number of drugs and indications, we primarily based our investigation on findings from systematic reviews of available RCTs (Randomised Controlled Trials) which mapped information on the drugs' added value. Our observations on (difficulties in calculating) cost-effectiveness are also based on findings from independent researchers published in *Health Technology Assessment* (HTA) reports.
4. Indications and time periods in which there is a (strong) increase in gross expenditure/average treatment costs, and no clear improvements in overall survival, may raise doubts about the efficacy in relation to survival (and also, therefore, their cost-effectiveness). In line with findings published in international literature, the analysis of the Belgian observational data indicates that automatically associating 'innovative' oncological drugs with a (great) added value in terms of patient survival is unjustified.
5. The independent economic assessments contained in the HTA reports suggest that the greatest uncertainty concerns the estimation of the effect of treatment on overall survival. This was largely due to the following reasons: a lack of studies directly comparing the intervention and the appropriate comparator(s) (*head-to-*

head studies), immaturity of study data, use of surrogate endpoints with an uncertain association with survival and quality of life, and also an occasional crossover of patients which distorts the *intention-to-treat* analyses.

6. Unfortunately, the effect on quality of life is also extremely uncertain. This is primarily due to a failure to measure or only partially measure the effect on quality of life during the comprehensive study follow-up (using a generic utility instrument for the economic evaluations) and/or the non-transparent reporting of the results for these estimates. In some cases, the results for this outcome are even deemed confidential, which should never be the case. Furthermore, the impact on quality of life is often not included in the systematic reviews identified.
7. Systematic reviews prove that the relationship between surrogate endpoints (such as *progression-free survival* – PFS) and critical patient outcomes, i.e. survival and quality of life, is generally weak. This scientific evidence reveals that the automatic use of surrogate endpoints in clinical and economic evaluations is problematic. Specific validation of these surrogate endpoints is required for the indications and drugs for which they are used.
8. RCTs remain the gold standard for estimating the treatment effect of an intervention relative to a comparator. Scientific studies show that observational data often provides inaccurate information for treatment effect estimates. The promotion of non-randomised database analyses as a quick source of "*real-world evidence*" related to treatment effect is a false solution.
9. In order to provide rapid access to innovative medicines, reimbursement decisions are increasingly making use of *managed entry agreements* (MEAs) at a time when uncertainties about the added value of these medicines still remain. In principle, this temporary reimbursement should allow time to provide the necessary evidence. Unfortunately, the system offers no incentive for providing reliable evidence in an effective way .
10. The prices agreed in these MEAs also remain secret, which presents an obstacle to setting more acceptable public prices. This makes the entire system opaque. Prices (for the intervention, the comparator and/or the subsequent treatments) are also confidential in almost all economic evaluations. In such cases, cost-effectiveness cannot be calculated independently.
11. There are two key junctures in the life cycle of a medicine that can be used as leverage for obtaining the required evidence; at the point of granting a marketing authorisation (European level) or the moment of awarding a reimbursement (national level).

SUMMARY

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Cancer medicine is becoming more and more expensive

During the past two decades, the pharmaceutical industry developed and launched an increasing number of medicines against various types of cancer. The majority of the new products in this category launched on the market are so-called "innovative medicines" (for example monoclonal antibodies or immune therapies) that the industry charges higher prices for than for traditional cancer medicine (chemotherapy or hormone therapy). These higher prices could be justified by their significant additional value. In the RIZIV-INAMI (NIHDI, National Institute for Health and Disability Insurance) budget, expenditure on these innovative products increased from approximately €140 million in 2007 to €403 million in 2016 and to €1 billion in 2019 (MORSE 2020 report).[1, 2] Currently, it represents the bulk of hospital spending on oncology drugs, well ahead of traditional cancer drugs.

It is problematic that the price of innovative medicine is not really based on the development costs of the product or the clinical benefit expected from it, but rather depends on what the governments are willing to pay to ensure that the patients in their country have access to it. There is thus also not necessarily a relation between the efficacy of a new product and the price of it.[3] This model of price setting leads to an upward spiral that creates a potential hazard even to wealthier countries with regard to the future financing of health care. The Organisation for Economic Co-operation and Development (OECD) estimates that global sales of cancer drugs will continue to rise in the coming years and is considering disconnecting these high prices from the objective health benefits of these products to the population as a major economic challenge for our societies.[4]

1.2. Are the benefits for the patient sufficiently proven?

The problem becomes even more complex because the benefits of these drugs are not always that great and the evidence of their added value is not always convincing. Innovative cancer drugs are expected to improve the life expectancy and/or quality of life of patients in comparison to traditional treatments. In reality the regulating institutions, such as the EMA in Europe or the FDA in the United States, which issues the trading licenses of the medicine, do not require clear evidence about the impact on life expectancy and the quality of life. In fact, their requirements regarding evidence about the efficacy and effectiveness have gradually decreased.[5]

Two recent studies (2017[6] and 2019[7]) systematically investigated the benefit of cancer drugs in the *European Public Assessment Reports* (EPARs)[a] that were published by the EMA when they received the trading license, as well as the data from the follow-up studies after launching on the market. The results of these studies are rather sobering from a scientific point of view. The first study[6] is an evaluation of 48 anti-cancer medicines (for 68 indications) approved by the EMA between 2009 and 2013. In only a third of the cases (24/68), the authors established a significant increase in survival. In addition, this extension - from 1.0 to 5.8 months (average 2.7 months) - was considered clinically significant in only 16% of the studied indications (11/68). Only 10% (7/68) of the cases provided proof of an improvement in quality of life.
In the post-marketing phase and after an average follow-up of 5.4 years (3.3 to 8.1 years), the authors could only see a significant improvement in the survival or the quality of life in 35/68 files; the same parameters were still uncertain more than three years later for approximately half of the medicines. The authors concluded that "most drugs entered the market without evidence of benefit on survival or quality of life. At a minimum of 3.3 years after market entry, there was still no conclusive evidence that these drugs either extended or improved life for most cancer indications. When

[a] A European Public Assessment Report (EPAR) is published for every application for a medicine for human or animal use for which a trading license can be granted or refused. This report follows on from the EMA's assessment of an application that was submitted by a pharmaceutical company.

there were survival gains over existing treatment options or placebo, they were often marginal."[6]

In the second study,[7] the authors identified 102 cancer medicines for which trading licenses were issued between January 2009 and May 2015. In 42% of cases (43 files) there were no data or no positive improvement in the average survival at the time of EMA approval. Three years later, these data were still absent for 28% of the medicines (29/102). Out of these, 17 were recognised orphan medicinal products, 6 were marketed subject to conditional approval and 25 were subjected to additional monitoring prescriptions.

We will return to this later (see chapter 6).

1.3. The confidentiality obligation makes the system even less transparent

In Europe, obtaining the marketing authorisation for a new medicine and the decision on whether to reimburse it - and at what price - are independent of each other. The marketing authorisation is normally issued by the *European Medicines Agency* (EMA) based on quality, safety and efficacy criteria. The reimbursement decisions remain under the authority of every member state. Every country performs their own evaluations and negotiates individually about the price with the companies.

More and more emphasis is being placed on the – otherwise very laudable – goal of giving patients faster access to the promised innovations. As a result, policy-makers are increasingly confronted with a reimbursement request for which there are still many uncertainties about the actual added value of the medicines. In order to make sure the patient is not denied access to the medicines, so-called *Managed Entry Agreements* (MEA) are used. The principle of these agreements is that a temporary reimbursement is granted for a period that should allow the identified uncertainties to be addressed, in exchange for significant - but confidential - discounts from the company (for more information on this subject, see the KCE 288 report). This system, which was initially intended as an exception, is now being used for a growing portion of medicines; €1.6 billion of expenditure in 2019[b] is covered by these secret drug contracts, of which approximately €600 million is refunded (see 6.2.1). In other words, the drug is rapidly marketed and reimbursed, while it is assumed that the company will conduct further clinical trials and provide data to confirm that the product does indeed deliver its added value. Unfortunately, once a drug is (temporarily) reimbursed, there are no incentives for pharmaceutical companies to continue their clinical trials (see 6.2.2). We are thus confronted with huge expenses for expensive medicine, of which the actual added value for the patients have not always really been illustrated. Moreover, this duty of confidentiality leads to an increasing lack of transparency of the entire system and therefore makes it increasingly difficult or even impossible to carry out economic evaluations of these medicines.

[b] On a total gross budget of €5.3 billion for speciality pharmaceuticals. After deducting the refunds (€600 million) and other taxes (€430 million), this amounts to a net cost of approximately €4.2 billion for medicines, of which a net €1 billion goes to medicines under contract.

2. RESEARCH QUESTIONS AND METHODS

2.1. Research questions

The original request of the NIHDI was to analyse the expenditure on innovative medicines in oncology in recent years and to determine a posteriori how useful these medicines have been. In other words, what concrete benefits have these expenditures brought to patients? If these benefits are significant, the expenses can generally be seen as justified. If, on the other hand, these benefits are limited, the question arises as to whether these expenditures have not hindered the financing of other, more (cost-)effective treatments, thus resulting in a so-called opportunity cost.

Initially, the first research question was whether the cost-effectiveness of recently reimbursed cancer drugs in Belgium could be calculated, taking into account the efficacy data reported in clinical studies (and any clinical effect observed in practice) and the expenditure of these drugs.[c] If that could be calculated, the second question was the total scope of the health benefits generated by these expenditures, as well as the overall average incremental cost-effectiveness ratio (ICER) of these drugs.

These questions are indeed fundamental. However, it is not possible to calculate a detailed cost-effectiveness ratio for each of these numerous cancer drugs. In addition, calculating an overall average cost-effectiveness ratio for an entire class of drugs would be difficult to interpret, as this ratio can vary significantly between drugs and the average obtained as a result could lead to erroneous conclusions.

The research questions were thus reformulated as follows:

- **What is the evolution of the overall survival in a wide selection of oncological indications and what is the budgetary impact of the reimbursement of new cancer drugs that have been marketed for these indications over the past 15 years?**
- **What is known in the literature about the benefits (for example consequences for overall survival and quality of life) and the cost effectiveness for a wide selection of new cancer drugs?**

We decided to focus our research on twelve types of **cancer (hereinafter referred** to as 'indications') for which relevant (Belgian) data on survival, costs, efficacy and cost-effectiveness could be collected. These indications were chosen in consultation with external experts / oncologists and stakeholders (see names in colophon). Combined, these indications are good for **an important part of the innovative cancer drugs that were launched on the market in the past 15 years.** Various cancer drugs were selected within these twelve indications. We decided to limit the list to the most commonly used and/or the drugs with the highest annual expenditure (excluding the most recent for which insufficient data are available). In total it concerns **40 innovative drugs.** The experts were expressly asked to supply "positive" examples (with a high expected added value) to the study group to give a balanced summary. The reader will find the twelve indications and the 40 selected drugs in Table 1.

[c] Only the gross expenses are known, as the repayment terms are laid down in secret contracts. We will return to this later on.

Table 1 – Selected oncological indications and medicines

Breast cancer (women)	pertuzumab, trastuzumab emtansine, palbociclib, abemaciclib, and ribociclib
Chronic myeloid leukaemia	imatinib, nilotinib, dasatinib, bosutinib, and ponatinib
Colorectal cancer	bevacizumab, cetuximab, panitumumab, aflibercept, and regorafenib
Head and neck cancer	cetuximab
Malignant skin melanoma	ipilimumab, pembrolizumab, nivolumab, dabrafenib, vemurafenib, and trametinib
Mesothelioma	pemetrexed
Multiple myeloma	lenalidomide, pomalidomide, bortezomib and daratumumab
Non-Hodgkin lymphoma	rituximab, ibrutinib and obinutuzumab
Non-small cell lung cancer	erlotinib, gefitinib, afatinib & crizotinib, nivolumab and pembrolizumab
Ovarian cancer	bevacizumab
Prostate cancer	enzalutamide
Cancer of the kidneys	sunitinib, pazopanib, everolimus, sorafinib, axitinib, temsirolimus, and nivolumab

2.2. How did we proceed?

2.2.1. Observational data

When we use the term "observational data" in this report, we refer to all data about the Belgian population that we could collect from the ***Belgian Cancer Registry*** (BCR), the **Intermutualist Agency** (IMA) and the **Crossroads Bank for Social Security**. It is thus a very reliable reflection of the actual situation in our country.

Box 1 – The Belgian Cancer Registry

The Belgian Cancer Registry collects data about all Belgian cancer patients. Hospitals and anatomopathology labs are required to report all newly diagnosed cancer patients to the registry. The following data are communicated: the patient's age at diagnosis, the date of incidence (date of the first histopathological confirmation or of the technical act leading to the diagnosis of cancer), the topography and histology of the tumour (ICD-O-3) and the clinical and pathological TNM stage.[d]

The Belgian Cancer Registry has a legal basis for the use of the unique patient identification number (national registry number or national number) so that the data from the IMA and the Crossroads Bank can be linked to the data from the cancer registry.

For the twelve selected indications, the BCR provided survival data (per stage if relevant) according to the year of diagnosis for the period 2004-2017. For some indications, we used data for Flanders that were available from the year 2000.

[d] Recently, an automatic transfer of selected biomarker results from the laboratories has also been provided by the labs (PITTER registration). These biomarkers also determine subgroups within certain cancers. Targeted cancer treatments are started based on such biomarkers. These details were not available for this study.

These data were linked with those from the Intermutualistic Agency (IMA)[e], which allowed us to have reimbursement data for each registered patient up to 31st December of the fifth year after the incidence year. For this study, we used IMA data for identifying the expenses for cancer medicine. However, we need to take into account a possible two-year delay before the IMA data can be considered as 100% complete. IMA data were available until June 2019. In view of the possible delay with performance declarations, this study only took registered performances until the end of 2018 into account. Where relevant, we have limited our study to patients who were in stage IV (metastatic cancer) at the time of their diagnosis, as they receive[f] the most innovative drugs, relatively speaking, and these drugs are normally used first at this stage.

The IMA provided the reimbursement data from the NIHDI per ATC category (*Anatomical Therapeutic Chemical Classification System*) for oncology drugs.[g]

The Crossroads Bank for Social Security provided information about the vital status of patients based on the unique social security identification number (INSZ). This method of active follow-up allowed us to follow patients until 31st January 2020. Therefore, we can present survival results of at least two years of follow-up for all included patients up to and including the 2017 incidence year.

By combining these different data, it was possible to calculate, for each type of cancer, the number of patients who received each of the innovative drugs studied, as well as the survival and relative survival observed, related to the incidence year. All methodological details are described in part 3.1 of the scientific report, and the results per indication are presented in twelve specific chapters of the same scientific report.

2.2.2. *Literature study*

We emphasise that **this report is not a classic HTA report** that focuses on a specific treatment for a specific oncology indication. This study focuses on the presentation of the Belgian observational data, on the results of previous systematic reviews on overall survival for the selected oncological indications and drugs, and on economic evaluations based on existing HTAs. No separate search strategy has been established for the most recent RCTs, and no meta-analyses have been updated and no specific adverse drug reactions have been analysed.

The search in the **medical literature** is mainly focused on recent, high quality reviews. The extracted data mainly relate to survival and quality of life. The research methodology is described in detail in part 3.3.1 of the scientific report.

For the assessment of **cost-effectiveness ratios**, we mainly relied on UK analyses. In England, the *National Health Service* systematically conducts *Health Technology Assessment* (HTA) studies for the innovative medicines that are placed on the market, and these studies are publicly available. The review of the economic assessments in these HTA studies was conducted by an independent *'evidence review group'* based on data submitted by the company. These HTA studies contain a critical analysis of the scientific evidence from the underlying RCTs. For the sake of completeness, we looked at some Belgian files and found that they contain more limited information than the transparent British evaluations. That is why we have decided to use the British files.

Although the prices (confidential or otherwise) that the UK cost-effectiveness studies are based on differ from the prices charged in Belgium, the clinical studies that form the basis for the researchers' assessments are the same. The analysis cannot therefore be fully translated into the Belgian context, but the critical assessment of the underlying international studies that the economic evaluations are based on is also fully applicable in Belgium. Moreover, it is not

---

[e] This link has been allowed since 2009; it concerns health insurance fund data on cancer-related diagnostic and therapeutic procedures and reimbursed oncological drugs (inpatient and outpatient).[8]

[f] Many cancers are treated locally (surgery, radiotherapy) in the early stages.

[g] It concerns the following classes: ATC level 2: 'L01'; ATC level 5: 'L02BA01', 'L02BA03', 'L02BB01', 'L02BB03', 'L02BB04', 'L02BG03', 'L02BG04', 'L02BG06', 'L02BX03', 'L03AC01', 'L03AX03', 'L04AX02', 'L04AX03', 'L04AX04', 'L04AX06'.

the aim of this study to come to explicit conclusions about the cost-effectiveness of a specific drug for a certain indication (which would be the case in a classic HTA study), but to address the problems of estimating the cost-effectiveness for a broad selection of cancer drugs.

The research methodology for the economic literature is described in detail in part 3.3.2 of the scientific report.

3. EVOLUTION OF THE OVERALL SURVIVAL AND BUDGETARY IMPACT OF THE INNOVATIVE MEDICINES

Here we provide a general overview of the evolution of survival in Belgium over the past 15 years for the twelve indications studied, but also of the evolution of the expenditure of the NIHDI on medicines for each of these indications in the same period. The detailed results of these analyses are contained in twelve separate sub-reports that the more interested reader can consult in part 4 of the scientific report.

3.1. Preliminary remarks

It should be noted in advance that the evaluation of the effectiveness of cancer treatments should also take into account other variables, such as the possible effect of a more accurate or earlier diagnosis, the introduction of screening programmes, progress in surgery and radiotherapy, and others. For example, an article published in the *British Medical Journal* in 2016 claims that the proportion attributable to drug treatments in improving the five-year survival of the most common cancers was no more than 2.5%. After all, most of the benefits in this area can be attributed to advances in early diagnosis and treatment.[9] However, this is especially true for cancers detected at an early stage, while innovative cancer drugs are generally first used in patients with advanced cancer for whom improvements in diagnosis and screening have comparatively less impact. Therefore, where possible, we limited our analysis to patients who had their first diagnosis in stage IV (metastatic cancer) because it is in this group that the innovative drugs are usually used for the first time. We assume that evolutions in other forms of treatment have changed the survival of these patients in a positive way and certainly not negatively.

Table 2 gives a general overview of the results of our analysis of observational data for the 12 selected indications for the incidence years 2004-2017. For every indication, there are four simplified graphs (the more detailed figures are included in the scientific report):

1. the observed survival probability one to five years after diagnosis
2. the median survival time
3. the total gross expenditure on cancer drugs for the first two years after diagnosis
4. the average expenditure on cancer drugs per patient for the first two years after diagnosis

With regard to survival, it is important to note that overall survival should not be the sole measure of effectiveness (and thus cost-effectiveness). The effect of treatment on quality of life should also be taken into account, which is not covered in these survival results. However, the measurement and reporting of quality of life in clinical trials for cancer drugs is frequently substandard. We will return to this later on.

With regard to expenditure, we have chosen to summarise it in this overview and for each indication by combining the evolution of the total expenditure on cancer drugs (depending on the number of patients) with the evolution of the average treatment costs for cancer drugs per patient, because we found that the price of the drug has a much greater impact on total expenditure than the number of patients treated. We also remind the reader that the data on expenditure in recent years may not always be 100% complete in this study (cf. possible delay of 2 years) and may therefore be an underestimate. Expenditures are also gross expenses, i.e. without taking into account refunds made under secret contracts, as due to confidentiality we cannot allocate these amounts to individual medicines in certain indications.

3.2. Summary of results

This section summarises the results of our analyses of the Belgian observational data (2004-2017). For more recent years, sufficient follow-up data on reimbursement and survival were not yet available. For each of the 12 indications, further details are available in the scientific report (part 4.1 to 4.12).

It is important to emphasise beforehand that the results presented do not make any statements about the impact of the use of specific drugs or about the situation of individual patients. It is up to the patient and the physician to engage in a dialogue so that an informed decision about treatment can be made.

For half of the studied indications (usually minor) improvements in survival are observed; these are almost always accompanied by major increases in gross cancer drug expenditure and average treatment costs.

Chronic myeloid leukaemia: survival has improved over the years. Spending on cancer drugs has doubled from €4.8 million in 2004 to €10 million in 2015. The average cost of treatment per patient already exceeded €40,000 in 2004 and rose to €64,500 in 2015.[h]

Multiple myeloma: Survival remained stable between 2004 and 2013, and tends to improve in the last incidence period (2014-2017). Total expenditure and the average cost per patient have steadily increased over time, from less than €2.5 million in 2004 to over €40 million in 2017, and from €5,300 in 2004 to €59,200 in 2017.

Non-Hodgkin's lymphoma:

- In the CLL/SLL subgroup[i], survival improved slightly over the years, while gross expenditure has increased fivefold, from less than €1 million in 2004 to €5 million in 2015. The average cost per patient increased from €3,300 in 2004 to €19,200 in 2016.
- in the DLBCL subgroup[j], survival increased slightly between 2004-2008 and 2009-2013; thereafter, no further improvement was observed. The

[h] Expenditure dropped in the last two years, presumably due to the expiration of the patent on imatinib in 2016.

[i] CLL/SLL: Chronic lymphocytic leukaemia/small lymphocytic lymphoma.

[j] DLBCL: Diffuse large b-cell lymphoma.

increase in total expenditure was relatively limited, from €6 million in 2004 to €7.7 million in 2016, and the average cost per patient remained stable at €12,000.

- in the mantle cell lymphoma subgroup, overall and relative survival did not improve. Expenditure on pharmaceuticals has increased fivefold from €0.8 million in 2004 to €4 million in 2016. Over the same period, the average cost per patient increased from €8,800 to over €30,000.

Stage IV non-small cell lung cancer: Survival of patients diagnosed in 2014-2017 appears to have improved compared to previous incidence years. Although there is no positive influence on the median survival time, there is clearly an improvement in the observed survival after one to five years. Until 2014, total expenditure increased from €5.1 million in 2004 to €23.6 million in 2013, with no improvement in survival. In the last incidence period, when survival appeared to be increasing, they have continued to rise sharply to over €77 million. The same trend is observed for the average costs per patient: from €4,100 in 2004, it increased to €13,200 in 2013 and to €36,000 in 2017.

Stage IV prostate cancer: Survival has slightly improved over time, coinciding with an increase in expenditure from €1 million in 2004 to €6.6 million in 2016. The average cost per patient increased from €2,300 in 2004 to €9,000 in 2016.

Stage IV renal cell cancer: We noted an improvement in survival for patients diagnosed between 2014 and 2017. This improvement was already preceded by a strong increase in total expenditure before 2014, from virtually non-existent in 2004 to €4.5 million in 2013 and then €6.5 million in 2016. The average cost per patient increased from €3,300 in 2004 to €29,300 in 2013, and increased further in the latter period to €46,200 in 2016.

No positive evolution for survival was seen for the other half of the studied indications, while gross expenditure on cancer drugs increased significantly.

Stage IV breast cancer (women): there is no significant improvement in survival, but there is a strong increase in gross expenditure (almost quadrupled to €16 million), as well as average expenditure per patient (tripled to €24,500 per patient) over the period 2004-2017.

Stage IV colorectal cancer: Survival has changed little over time, while drug expenditure has increased from less than €10 million in 2004 to €20-24 million since 2009. Average expenditure per patient also increased from €10,600 to over €18,000 over the same period.

Stage IV head and neck cancer: Survival has not changed significantly over time. On the other hand, gross expenditure and average treatment costs per patient have increased significantly, from €420,000 (2004) to €5.5 million (2016) and from less than €1,000 per patient (2004) to more than €8,000 (2016), respectively.

Melanoma stage IV: no clear positive trend in survival has been observed over the years. Spending on its part has risen sharply, from almost nil before 2011 to more than €3.2 million in 2016. The average cost per patient, which was less than €1,000 before 2011, rose to almost €100,000 per patient in 2016. We note that we did find a positive evolution of survival for stage NA[k] patients.

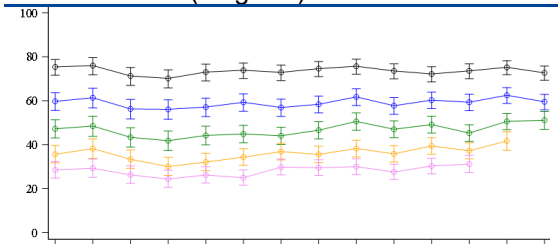
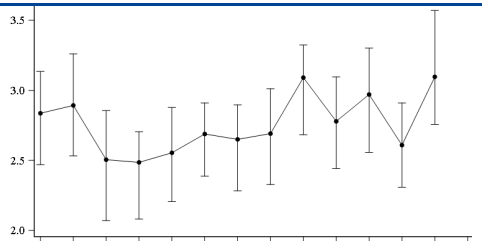
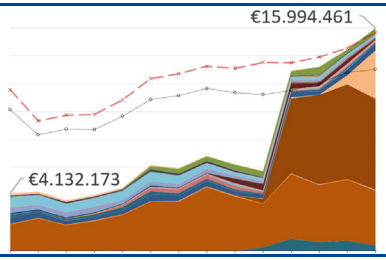
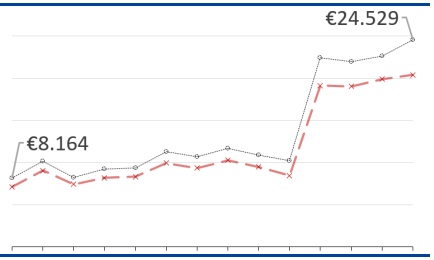
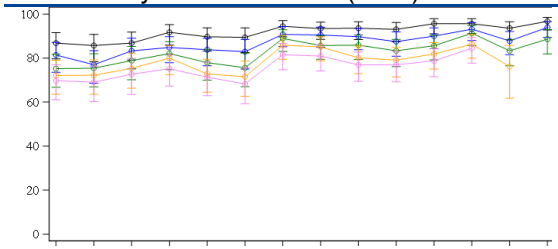
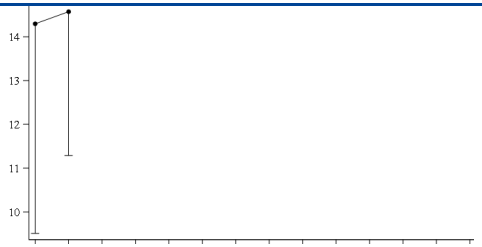
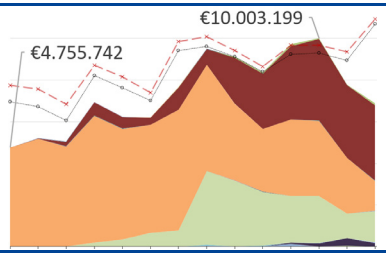
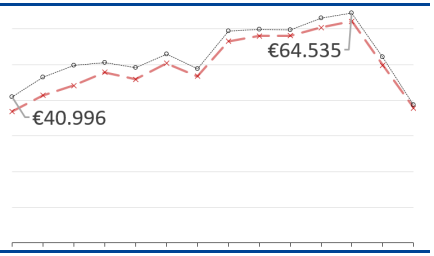
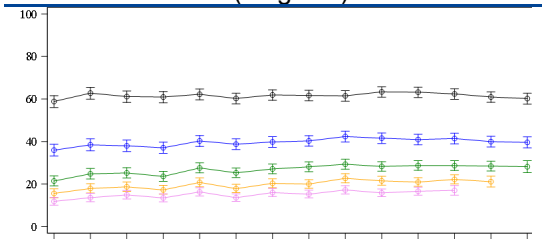
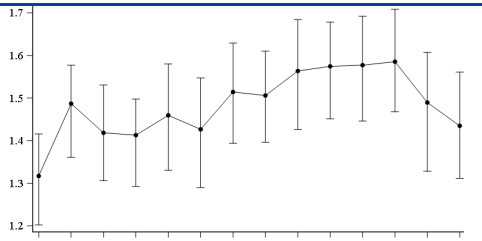
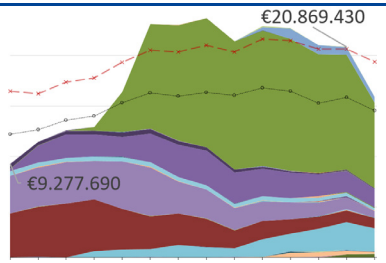
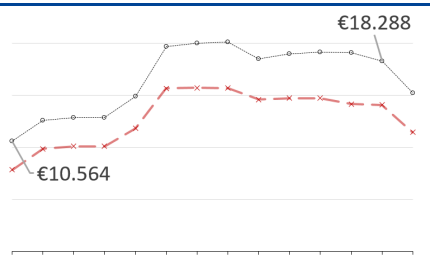
Mesothelioma stage III/IV/X: no apparent improvement in survival. Specific Flemish data have also been analysed (from the incidence year 2000); these also show no positive effect on survival. In contrast, we see a significant increase in gross expenses, from €103,000 in 2004 to €1.6 million in 2015. The average cost per patient increased from €2,500 in 2004 to €16,000 in 2015.

[k] If the location of the primary tumour is not known, no stage can be assigned, hence 'stage NA' (not applicable).

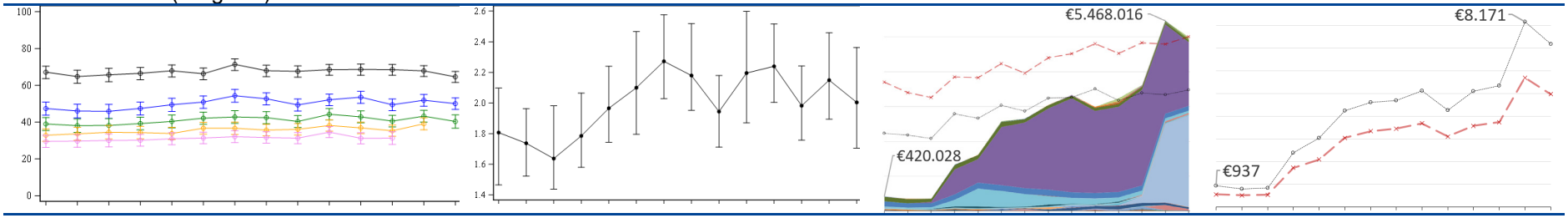
Stage IV ovarian cancer: No improvement in survival has been observed. Gross expenses have increased sharply from less than €1.5 million before 2013 to €4 million since 2014. The average cost per patient has more than doubled, rising from €12,500 in 2004 to €26,200 in 2016.

Conclusion: For the indications where there is a (strong) increase in expenditure without a clear improvement in survival, it is justified to question the effectiveness and also the cost-effectiveness of the drugs concerned.

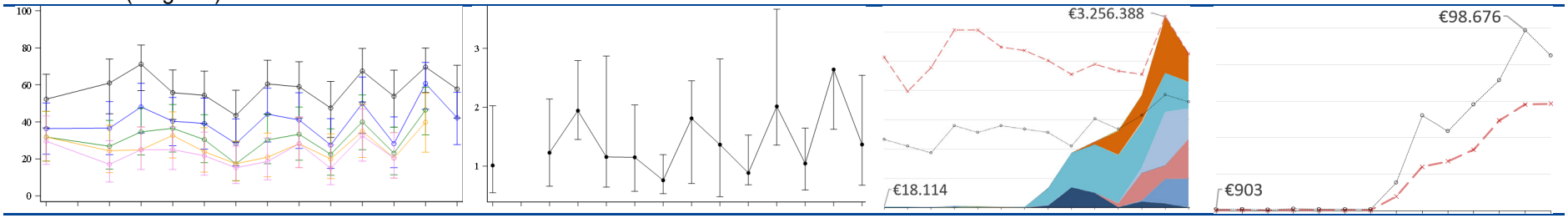
Table 2 – Overview of observational data for 12 indications of cancer (by incidence year between 2004 and 2017): 1st column: Change in survival probability observed from 1 to 5 years (%) - 2nd column: median survival time (in years) - 3rd column: total gross cancer drug expenditure for the first two years after diagnosis - 4th column: average gross cancer drug expenditure per patient for the first two years after diagnosis

Tumour type				
Breast cancer (stage IV)				
Chronic myeloid leukaemia (CML)				
Colorectal cancer (stage IV)				

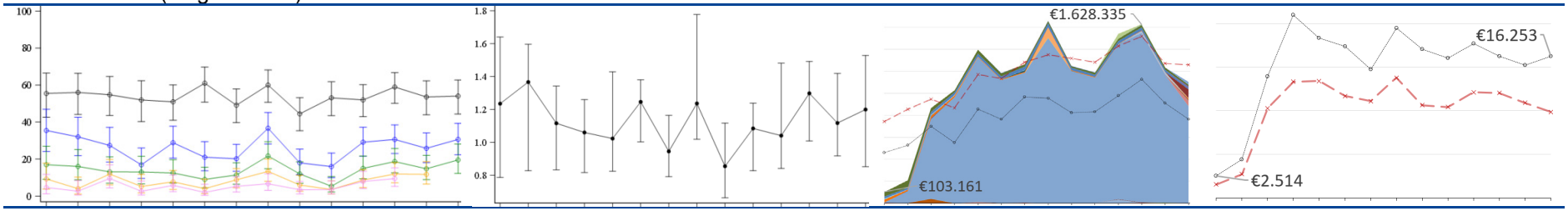
Head and neck (Stage IV)



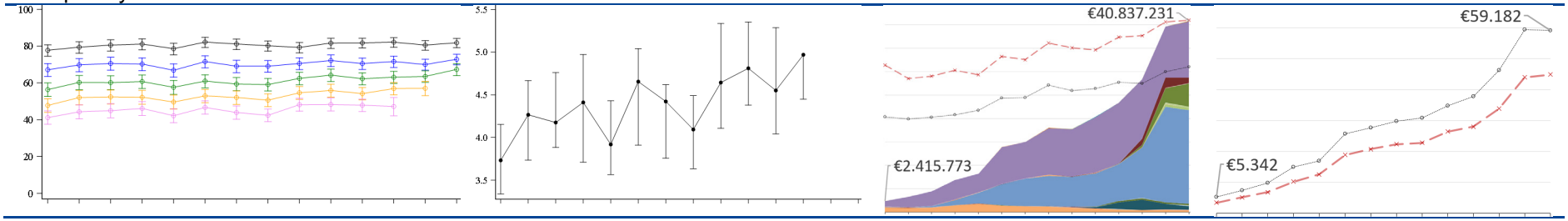
Melanoma (stage IV)



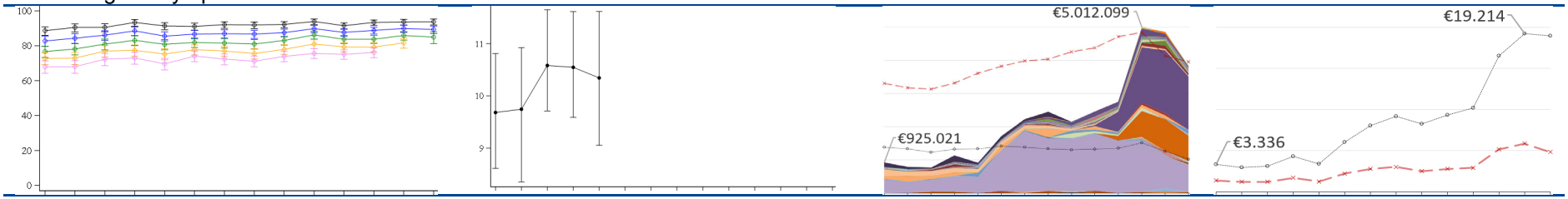
Mesothelioma (stage III/IV/X)



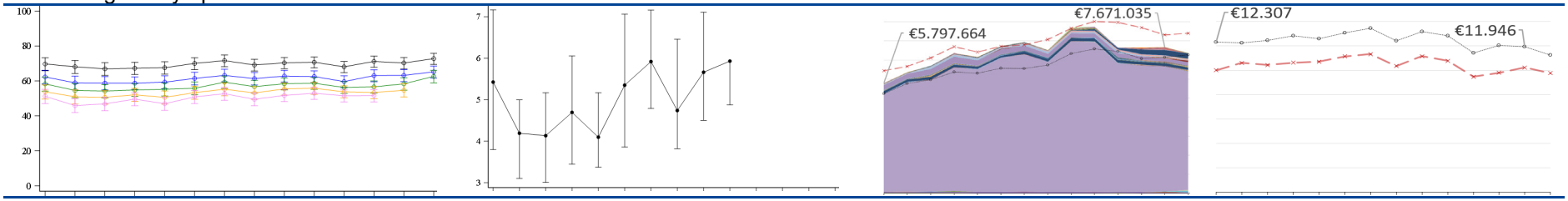
Multiple myeloma



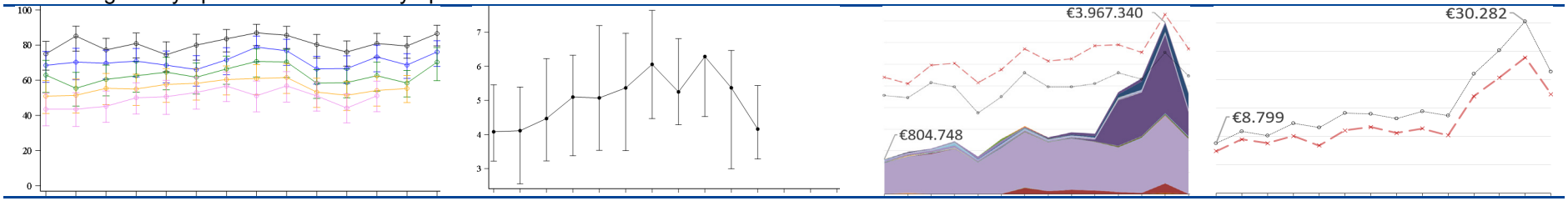
Non-Hodgkin's lymphoma: CLL/SLL



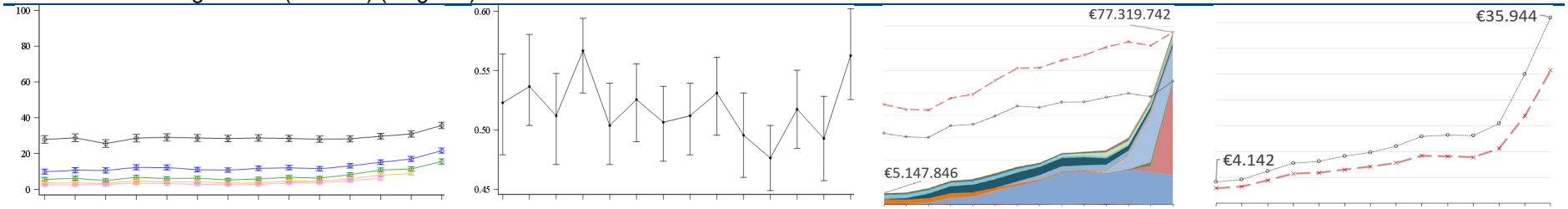
Non-Hodgkin's lymphoma: DLBCL



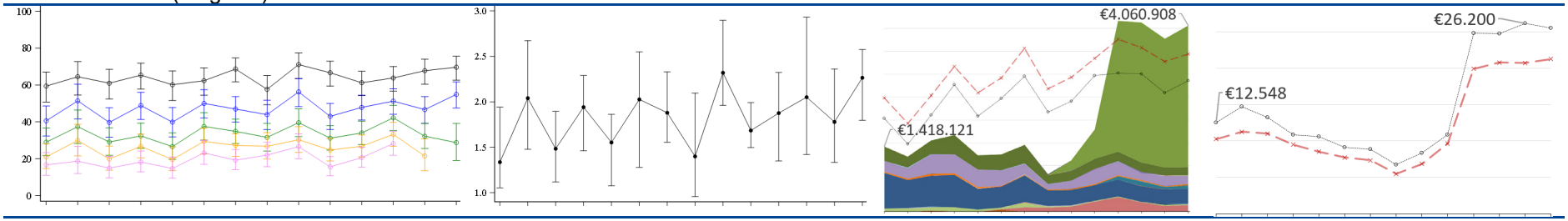
Non-Hodgkin's lymphoma: Mantle cell lymphoma



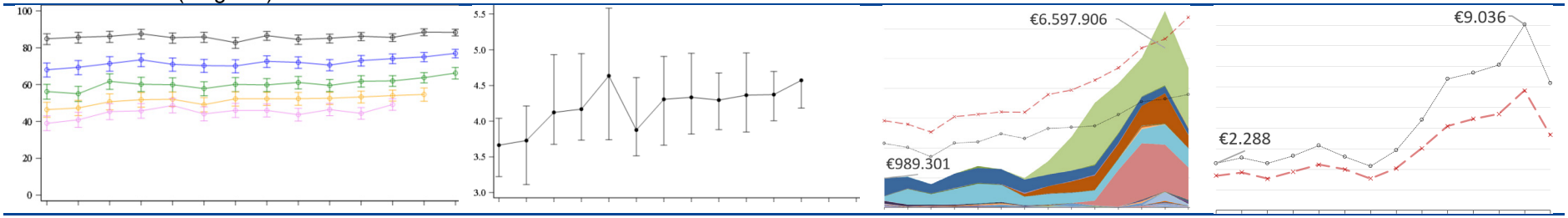
Non-small-cell lung cancer (NSCLC) (stage IV)



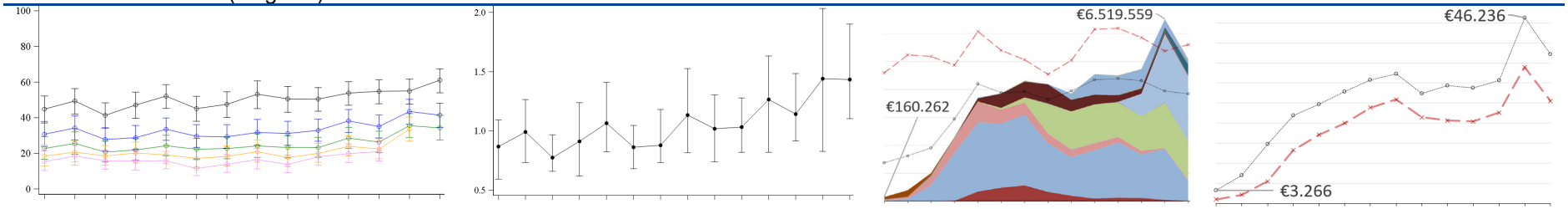
Ovarian cancer (stage IV)



Prostate cancer (stage IV)



Renal cell carcinoma (stage IV)



Further explanation of the figures: all x-axes show the incidence year 2004-2017. The y-axis shows the following: 1st column: observed survival probability (%); 2nd column: median survival (in years), if sufficient follow-up; 3rd column: cancer drug expenditure during the first two years after diagnosis (red dotted line = total number of patients in this indication, grey line = number of patients with cancer drug expenditure); 4th column: average cost per patient for cancer drugs during the first two years after diagnosis (the red dotted line expresses this in relation to all patients in this indication; the grey line expresses this compared to the number of patients with expenses for cancer drugs). For more detailed information we refer to the scientific report.

4. RESTRICTIONS OF OBSERVATIONAL DATA

Please note that the above results are based on observational data, and no causal relationship can be inferred in any way. For example, we cannot confirm that an improvement in survival is related to the use of a particular drug, because other aspects of care may also have improved during the same period. Conversely, the lack of improvement may also be related to characteristics of the affected populations (e.g. comorbidities) that could mask the effect of the treatment.

It is also possible that the effect of a drug is not seen in the general observational results because only a proportion of patients receive that treatment. For example, in stage IV breast cancer, the reimbursement of certain drugs is limited to specific subgroups based on the presence or absence of HER2 receptors on the tumour. However, this information was not available in the BCR data until recently. The costs cannot be identified specifically for this subgroup, but the budgetary impact of the use of these medicines is clearly visible in the general indication.

The population of the selected indications is also not necessarily comparable over time. For example, the introduction of screening and/or improved diagnostic procedures may lead to some cancers being detected earlier, which will improve the prognosis, but, as mentioned, this can be assumed to have less impact on stage IV cancer diagnoses. Death from causes other than cancer (e.g. cardiovascular disease) can also affect the level of survival observed. This is partially offset by the relative survival probabilities, which only consider excess cancer mortality. For this, however, correction is also only possible for factors that are measurable and registered (see 6.1.1). The results for relative survival probabilities are similar and are presented in the appendix to the scientific report.

Finally, we recall that the most recent cancer drugs were not taken into account in this study, although this field is evolving rapidly. Our observational data are limited to the incidence year 2017 (excluding the follow-up data, which go up to 2019). Such a delay is currently still unavoidable. However, the recommendations we formulate based on the available data from the past also remain applicable to current and future treatments. We therefore cannot simply assume that "innovative" medicine lead to major improvements in the survival and/or quality of life of the patients.

As already mentioned, the expenses mentioned in this report are gross expenses. Confidential discounts could not be included in our figures because we have no information to allocate refunds and taxes obtained to specific drugs. However, they do exist, so the actual net expenditure may be significantly lower.

5. COST EFFECTIVENESS

It is not the purpose of this summary to present the details of the economic evaluations performed for each of the selected individual oncology drugs in the specific indications. The interested reader will find more detailed information in the 12 specific chapters of the scientific report. We will limit ourselves here to a very general summary of the findings of our analysis of the economic literature.

We noticed the following elements, which will also be explained in more detail in chapter 6:

- Virtually all recent HTA evaluations are based on confidential prices for the intervention and/or comparators and follow-up treatments, which makes a realistic calculation of ICERs[l] impossible (see also 6.2.3). This applies in the first place to independent researchers who are not aware of the discounts granted. This confidentiality is problematic even for pharmaceutical companies, as they do not have access to information about discounts applied to the comparator and/or follow-up treatments from other companies. The ICER calculated by the pharmaceutical company in the application file is therefore not always the ICER that the reimbursement decision is based on. HTA evaluations that are not based on confidential prices are mostly older evaluations.
- Virtually no evaluations lead to the conclusion that an intervention is cost-effective based on public prices. When interventions are recommended, it is usually on the condition that confidential price discounts are applied.
    - Analyses conducted in the UK sometimes conclude that a medicine is acceptable, although its ICER is above the normal threshold applicable in the UK. The argument for these exceptions is often that the product meets the so-called 'end-of-life' criteria[m]. Certain products whose ICER remains very high and even above the specific threshold for drugs that meet the end-of-life criteria are nevertheless recommended for the Cancer Drugs Fund in some cases.[n]
    - It is exceptional that explicit reference is made to lower ICER thresholds due to uncertainties in clinical evidence and cost-effectiveness. This is particularly the case in the TA569 study (2019),[10] in which the researchers state that due to the uncertainty in the evidence on clinical efficacy, estimates of cost-effectiveness are highly uncertain. Given this uncertainty, the researchers do not consider an estimate above £20,000 per quality-adjusted life year (QALY) gained as a cost-effective use of NHS resources.
- Here, too, the confidentiality of prices makes it impossible to verify whether policy makers have paid a "correct" price in relation to the added value of the drugs studied. This lack of transparency also dilutes the accountability of policy makers, as it becomes impossible to know whether, for example, a higher price was paid for a product with no added value, or whether a limited or unknown added value is reflected in the price paid.

---

[l] The incremental cost-effectiveness ratio (ICER) is the ratio of the difference in costs and the difference in effects between an intervention and the comparator(s).

[m] The end-of-life criteria can be applied for treatment 1) for patients with a short life expectancy, normally less than 24 months; 2) where there is sufficient evidence to indicate that the treatment provides a prolongation of life, normally of at least 3 additional months compared to current NHS treatment, and 3) the treatment is applicable to small patient populations. The end-of-life criteria allow the ICER threshold to be raised from £20,000 - 30,000 per QALY applied in the UK (to £50,000 per QALY).

[n] The Cancer Drugs Fund (CDF) provides interim funding for drugs, making them available more quickly. Five conditions must be met: 1) the drug is not recommended for routine use because of clinical uncertainty; 2) the drug has plausible potential to be cost-effective at the current price, taking into account end of life criteria; 3) data collection can reduce clinical uncertainty; 4) ongoing studies will provide useful data; and 5) CDF data collection is feasible.(source: www.nice.org.uk)

- The greatest uncertainty in all of these evaluations is the effect of the drug on overall survival (see also 6.1.2); this uncertainty is mainly due to the lack of comparative studies between the intervention and the comparator(s), the use of immature data, the ambiguous relationship between the surrogate endpoints (e.g. *progression-free survival* – PFS) and the final endpoints (overall survival and quality of life) (see 6.1.4), or bias in the intention-to-treat analyses due to crossover of patients.
- There is also great uncertainty about the effect on quality of life. The calculation of the QALYs is often problematic, because the quality of life measurements in the underlying clinical studies have rarely been performed using generic utility instruments (see 6.1.5).
- Together with the effect on survival, the price of the intervention is a significant variable to determine the cost-effectiveness. The fact that the discount applied is unknown (for the medicine to be evaluated but also for the comparator) thus leads to great uncertainty in the cost-effectiveness ratio.
- The choice of comparator can strongly influence the calculation of the incremental costs, the incremental effects, and the ICER (see 6.1.3).

We can conclude that based on our observations we often find no or only limited improvement in overall survival, a strongly increased gross expenditure on cancer drugs and problems in the economic evaluations. These problems are due to uncertainty about the added value of these drugs on survival and quality of life, as well as the confidential and obscure prices that are paid for them.

6. WAYS TO BETTER ASSESS THE ADDED VALUE OF INNOVATIVE MEDICINES IN THE FUTURE

"When expensive drugs that lack clinically meaningful benefits are approved and paid for within publicly funded healthcare systems, individual patients can be harmed, important societal resources wasted, and the delivery of equitable and affordable care undermined."[6]

The findings in this study, based on Belgian data on overall survival and expenditure on innovative oncological drugs, may seriously question the efficient use of available resources in the reimbursement of these drugs. Despite the sharply increasing gross expenditure, there are no or relatively limited positive developments in survival in the twelve oncological indications examined. And for the impact on quality of life, the results in clinical studies are not always properly measured and/or reported.

The clinical and economic assessments found in the literature also do not allow to confirm the added value and thus the cost-effectiveness of many of these new drugs. Because the actual benefits for the patient are increasingly uncertain in the clinical studies, which serve as the basis for the applications to market these innovative medicines, it is becoming increasingly difficult to carry out *Health Technology Assessment* that are sufficiently substantiated to guide reimbursement decisions.

Ultimately, it is to be feared that the benefit for the patient will gradually play a less clear role in the marketing authorisation and reimbursement of innovative medicines. The balance between 'rapid to market' and 'demonstrating added value for the patient compared to existing treatment(s)' currently seems out of balance and leans towards the first argument.

We have tried to identify the main reasons for this actual situation, and we propose some recommendations to improve this situation, certainly in Belgium as well as on a European level. These reasons are partly related to the **uncertainties related to the clinical studies** that the policy decisions are based on, but also to the **decision-making process itself**.

This synthesis summarises our main findings; the interested reader can read the full analysis in part 6 and 7 of the scientific report.

6.1. Uncertainties in clinical studies

6.1.1. Randomised controlled studies remain the 'golden standard'

The gold standard for demonstrating the effectiveness of a treatment is the *randomised controlled trial* (RCT), because only randomisation can neutralise the influence of unknown variables on treatment outcome. A common criticism of RCTs – apart from the high cost – is that these studies do not reflect the heterogeneity of the real target population, and that it is very difficult to generalise their results to everyday practice. Observational studies do not have this drawback, as they are based on analyses of real-world-treated populations. However, that doesn't mean observational studies can replace RCTs to determine the effectiveness of new treatments, as some are suggesting today.

After all, **in observational studies**, in which, for example, cancer registry data is linked to administrative data at the population level, there is **no randomisation**. When the expected effect is very large, a non-randomised study can be convincing. On the other hand, it can be a major disadvantage if the expected effect of the treatment is not great and therefore difficult to demonstrate. In particular, the lack of randomisation can lead to misleading associations of a treatment with favourable outcomes, without a causal relationship, or, on the contrary, with apparent negative outcomes when the treatment does have clinical effects. The main stumbling block in the absence of randomisation is **selection bias**, i.e. a certain treatment is given more or less to certain patients (not always consciously) based on parameters such as the severity of the disease or the presence of co-morbidities. One example given by Banerjee and Prasad[11] is that there is a tendency to reserve aggressive treatments for the least ill candidates. As a result, those treatments are associated with better outcomes, and there is a tendency to conclude that they are more effective. In reality, the better outcomes of these treatments are influenced by the fact that they are given to patients who are healthier to begin with. The authors indicate that aggressive treatments that produce favourable outcomes in observational studies generally produce a clinical benefit in fewer than one in two cases.[11, 12] Other variables not included in the cancer registry data, such as obesity, tobacco use or certain co-morbidities, can influence treatment decisions and affect survival independently from the treatment chosen. Such selection bias cannot be corrected by statistical techniques, which was also shown in studies comparing results from RCTs and observational study results.[11, 12] Observational studies should therefore not simply be presented as a substitute for a well-designed RCT for estimating treatment effects.

There is likely no ideal study model that provides reliable evidence of efficacy quickly, as cheaply as possible and with exposure of as few patients as possible. **Randomisation remains the gold standard in cancer treatment research for the time being**. This does not exclude the role that observational studies can play, for example to clarify prognostic issues, investigate patterns of use in practice, and detect rare side effects or salient variations in care practices.[11]

Against this background, the current problem with the RCTs that form the foundation of the approval and reimbursement decisions for innovative drugs **is that they are not always appropriately designed to study the clinical benefits that patients and their caregivers expect, i.e. longer survival and/or improved quality of life compared to existing treatment(s).** This is further explained in the following paragraphs.

6.1.2. Survival is not always the primary outcome measure

For patients, the main outcomes expected from cancer treatment are an increase in remaining life expectancy or an improvement in quality of life, preferably both together. **It is therefore these *endpoints* that are ideally used as the main outcome measures in clinical trials** before a medicine is placed on the market or before a reimbursement is requested.

However, measuring the impact on survival requires a longer follow-up period, which would significantly extend the duration of clinical trials and delay patients' ability to access drugs. Therefore, surrogate endpoints are often used, which require extrapolations to be made to calculate the impact on overall survival. However, the use of these surrogate endpoints is highly debated, as for many indications it has already been shown these

surrogates have a low association with the impact on survival and quality of life. We will return to this later on (see part 6.1.4).

In the analysis of Davis *et al*.[6] of data in EMA approval applications, approximately a quarter of the clinical trials underlying the marketing authorisations were designed to select life extension as the primary outcome measure. Other studies included an assessment of survival as a secondary outcome but did not always have the statistical power needed to detect significant differences between the groups.

There are arguments that can be used to indicate that overall survival may or may not be used as an endpoint in a clinical trial. A first argument is that an RCT with survival as end point makes the study more expensive because the follow-up takes (much) longer. In patients with stage IV cancers, where innovative drugs are usually introduced, it is usually possible to identify the impact on survival within an acceptable time frame, because survival in these populations is unfortunately often short. A second argument is that more patients are needed in the trial to demonstrate an effect, which increases the costs of the study. However, the usefulness of a less expensive study that does not provide the desired information can be seriously questioned. This expenditure must also be weighed against the social expenditure for the reimbursement of cancer drugs, for which the added value is often uncertain, as well as the profit made by the companies. It is important for patients, doctors and society to know the real impact on the most important outcomes. A good measurement is therefore necessary, even if it poses a risk to the producer, who may not be able to demonstrate a significant effect on these endpoints that matter most.

Interpreting the survival results is often further complicated by the inclusion of crossover (transition of patients from the control group to the experimental group). The benefit argued by some researchers for including this crossover is that all patients can receive the new, supposedly effective treatment. The problem is that this can dilute the potential survival benefit of the therapy. The argument some use is that if the trial shows little or no survival benefit, it is because of the crossover. Here, too, sufficient nuance is needed and a distinction must be made between appropriate and inappropriate crossover (see Box 2).[13] If no or only a small effect on survival is established due to optimal follow-up treatment (i.e. appropriate crossover), then that is a correct determination of the limited added value of the intervention.

Box 2 – Desirable and undesirable crossover

Some crossover is desirable or suitable. For example, if a drug has already been approved for a later treatment (e.g. 2nd line), and is being evaluated for an earlier treatment (e.g. 1st line), the study should include the crossover. This is appropriate crossover.[14, 15] Not incorporating crossover in this setting would indeed harm participants in the control arm, because they would not receive the optimal post-progression therapy. However, for a drug that has never been approved for a condition, a crossover is generally undesirable.[14-16] Since the efficacy of the new drug is unknown, there is no ethical argument for administering the drug to patients in the control arm.[16] In addition, such crossover undermines the ability to determine the impact of the intervention on survival. It also delays the start of proven subsequent treatments. For these reasons, crossover in this setting is discouraged by the EMA and the FDA.[17, 18]

6.1.3. New medicines are not always compared with the right treatment

To effectively measure the added value of a new treatment, an RCT must include a comparison with a group of patients receiving the usual best available care (which can hopefully also be considered cost-effective). For example, when an active treatment is considered to be cost-effective in practice, a comparison with a placebo will lead to an overestimation of the added value of the treatment. The selection of the control group strongly influences the cost-effectiveness calculations, both by incorrectly excluding a comparator that is more cost-effective, and by comparing the intervention with an alternative that is less cost-effective.

Between 2006 and 2016, more than half of the EMA's conditional marketing authorisations for cancer drugs were based on studies without a control group (*single-arm*).[19] At the US *Food and Drug Administration* (FDA), fewer than one in five studies included active controls between 2005 and 2012.[19] For the registration of a drug, where the benefit-risk balance of a drug is considered, this information may be sufficient, but for doctors, patients and policy-makers who have to make a comparison with the standard

treatment(s), it is necessary to have better information about the added value compared to these standard treatment(s).

6.1.4. The outcome is measured by surrogate endpoints

As mentioned previously (see 6.1.2), essential outcomes, such as overall survival, are very often replaced by surrogate endpoints, such as 'progression-free survival' (PFS, i.e. the time between randomisation and relapse of the disease). These surrogate endpoints can be measured faster than survival, reducing the duration of clinical trials and significantly lowering their costs.

Surrogate endpoints do show that the product has a biological effect, but they often do not provide reliable information on clinical outcomes such as overall survival (or improvement in quality of life – see section 6.1.5). What they measure is therefore in many cases far removed from what is really important for the patients (see Box 3). More than 80% of the clinical studies leading to the approval of innovative cancer drugs in the US were based solely on such surrogate endpoints.[20] It is important to know which surrogate endpoints are reliable for which interventions in which indications. The current scientific literature shows that there are many indications where the association between the surrogate endpoint and survival and quality of life is weak. Policy-makers and patients need to be better informed about the true value and significance of surrogate endpoints.

Box 3 – Validate Surrogate Endpoints?

The use of a surrogate endpoint can be defended provided that an improvement in this surrogate endpoint actually translates into an improvement in the final outcomes (survival and quality of life). If this connection is sufficiently proven, studies can yield results more quickly. The EUnetHTA guideline recommends the following: “If progression-free survival (PFS) is used as an endpoint there should be sufficient independent evidence to demonstrate that this is associated with overall survival. … Overall survival is the gold standard for demonstrating clinical benefit and as such should be used where possible. … In the metastatic setting, data on PFS alone is insufficient and should be coupled with quality of life assessment and survival data, the maturity of which will be considered on the case by case basis.”[21]

An important problem is that more and more studies show that the association between the surrogate and final endpoints is weak. Two systematic reviews show disappointing results. The study by Ciani et al. showed that the strength of the association between the surrogate endpoints and survival was generally low. The available evidence varied considerably by cancer type and by evaluation method, and was not always consistent even within one specific cancer type.[22] The second systematic review by Prasad et al. concludes that most validation studies of surrogate endpoints in oncology find low correlations with survival, and therefore the evidence supporting the use of surrogate endpoints in oncology is weak.[23]

Another study by Gyawali et al.[24] sought correlation studies of surrogate endpoints of survival in breast cancer that the FDA deemed appropriate for (accelerated or normal) approval: *event-free survival* (EFS), *disease-free survival* (DFS), *objective response rate* (ORR), *progression-free survival* (PFS) or *pathological complete response rate* (pCR). However, these studies show that none of these measures (including PFS) correlates strongly with the effects of treatment on overall survival. Even if a surrogate endpoint can be sufficient for drug registration (EMA & FDA), it is problematic for a national policy-maker when making reimbursement decisions, as well as for the physician and patients, to correctly estimate the real added value.

Again, the required nuance is necessary here. If the surrogate endpoints are validated, their use can be justified. It is important to not only look at individual studies, but at reviews and meta-analyses to avoid bias. For any new drug with a clearly different mode of action than its predecessors, it is necessary to reassess the surrogate endpoints used, and validate them specifically for each indication and intervention.[25] After all, it must be possible to provide evidence of the fact that the surrogate endpoints reliably predict the effect of treatment on the clinical parameters.[26]

Finally, we emphasize that not only the association but also the size of the association is important. In some economic evaluations, PFS is used as a complete surrogate for survival. There is virtually never any scientific evidence to support these kinds of assumptions. In one case, the independent UK Evidence Review Group had looked at this ratio and found that there was not a 1-to-1 ratio as stated in the economic evaluation, but rather a ratio of 38.5%. It goes without saying that such assumptions give a distorted and too optimistic picture of the (cost-) effectiveness, and give wrong information to policy makers.

Could surrogate endpoints therefore play no role at all in marketing authorisation and reimbursement decisions? Is there a solution to combine rapid market entry with reliable data on overall survival and quality of life? The implementation of RCTs measuring overall survival and quality of life is a necessary first step. A **phased system** that makes it possible to bring innovative oncology medicines to the market while ensuring comparative data are collected as quickly as possible is a feasible option. This would mean that comparative studies can be started in **the pre-marketing phase** (6.2.2.1), and that these studies, after a surrogate effect is identified, can be continued under a form of **conditional reimbursement** (6.2.2.2) until overall survival can be effectively assessed.

6.1.5. Quality of life is one thing that is often overlooked in clinical studies.

6.1.5.1. What does the literature say?

In their study, Davis *et al*. noted that none of the studies supporting the approval of 48 oncology drugs by EMA between 2009 and 2013 included *Quality of Life* (QoL) assessments as a primary endpoint.[6] This is hardly surprising, as the EMA does not require such assessments, even for medicines for incurable cancers. And while 54% of the studies analysed by Davis *et al.* rated quality of life as a secondary outcome, only 10% reported any significant improvement for this parameter.

The same authors also noted great heterogeneity in the way quality of life outcomes are reported. For example, some outcomes presented as significant are, in reality, only significant for individual parameters or sub-dimensions of the scales used. In addition, it is difficult to determine whether statistically significant improvements in quality of life are clinically relevant. In other words, the benefits to quality of life are often far from proven, so Davis and his colleagues conclude that their outcomes – however limited – may be an overestimation of the proportion of innovative drugs that provide real quality-of-life benefits.

These findings are particularly troubling because many innovative oncology drugs (including those selected in this study) have been approved for advanced metastatic disease, with palliative objectives – i.e. to improve quality of life – or to extend lifespan, ensuring that one must be careful that the survival gain is not negated by treatment-related deterioration in quality of life.

6.1.5.2. And our own study?

We also paid particular attention to how QoL outcomes were measured in the studies underlying the approximately 100 HTA reports analysed as part of our study. We were particularly interested in using **generic utility instruments**, as recommended by EUnetHTA. Indeed, the use of generic utility instruments enables a standardised conversion of the outcomes into "QALYs gained" (quality-adjusted life years gained), an essential parameter for economic evaluations.

The guidelines of EUnetHTA[27] generally recommend a combination of a disease-specific QoL measure and a generic QoL measure to assess the impact of the disease and the impact of treatment on quality of life as accurately as possible. This impact can be negative (e.g. due to treatment-related side effects) or positive (e.g. delay in the deterioration in quality of life).

Here are the key findings from our analysis of economic evaluations related to the measurement of quality of life:

- A large portion of the studies do not include a direct comparison of the intervention with the standard treatment as a control group;

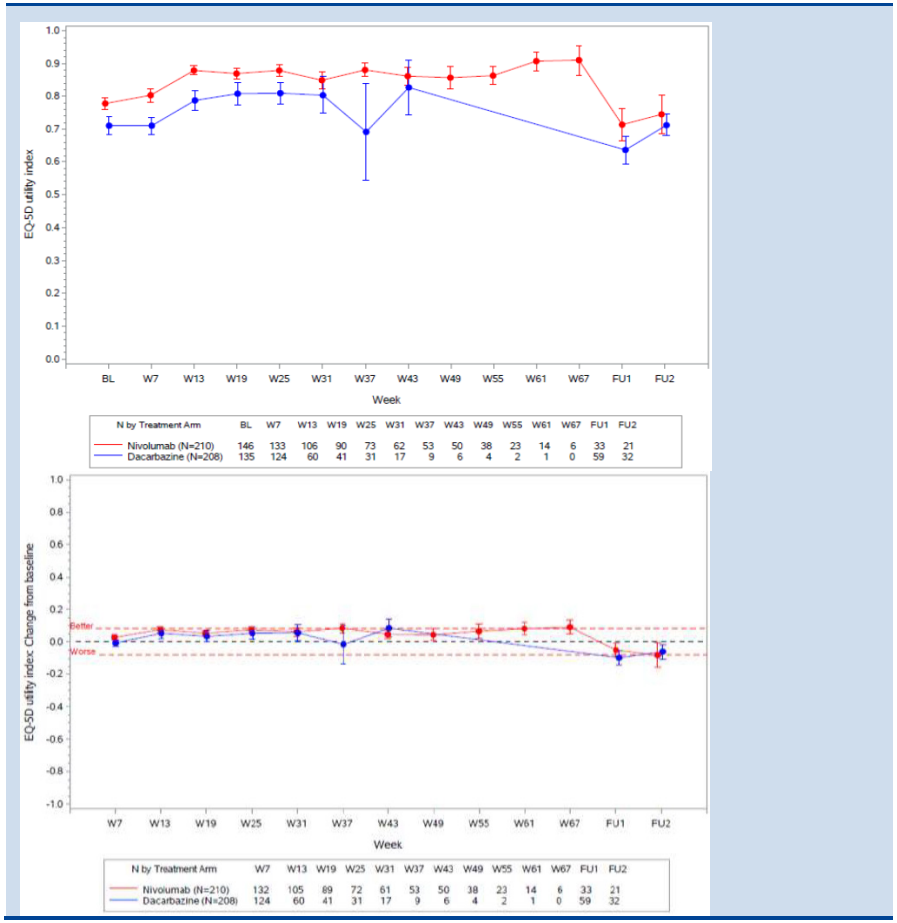
- When making a direct comparison, a generic utility instrument for QoL measurement is rarely used;
- In studies using the EQ-5D, we see that:
  - No measurements are taken during the entire follow-up period of the study. The questionnaire is generally no longer completed when the disease has progressed, which is exactly the moment when significant changes in quality of life can be expected.
  - The outcomes are generally not reported in a transparent manner (i.e. for both treatment groups, at all measurement moments, and indicating the uncertainty surrounding the central values). In some cases there is only a rather vague general statement, for example "the quality of life scores show no clinically significant change from baseline or compared to the other treatment group" (see example in Box 4).
  - In fact, several reports consider the details of the quality-of-life outcomes to be confidential.
- The results of the EQ-5D are not always directly used in economic models.
- In virtually all studies, researchers try to relate the measurements of the EQ-5D to include utility[o] in their economic assessment. The utility is often obtained from indirect sources (and not directly in the main clinical study by using a generic QoL measurement tool). The link is created by making assumptions about quality of life relative to the patient's disease state (e.g. progression-free survival, disease progression and death).
- In some cases the information was even based on studies where other medicines were administered. This does not always take into account side effects that may accompany specific treatments.

In addition to the great uncertainty about the impact on survival, there is often a lack of reliable information about the impact on quality of life, which prevents a reliable calculation as to cost-effectiveness. Here, too, a good measurement of quality of life is a basic requirement for making a reliable clinical and economic evaluation.

[o] a QoL score on a scale where 1 represents perfect health and 0 represents death.

Box 4 – Example of (non) transparent reporting about the QoL

An economic assessment presented by a pharmaceutical company compares product A (new) to product B in patients with advanced melanoma. The EQ-5D utility scores and the EORTC QLQ-C30 global health status are better for A than for B at baseline and throughout the observation period. However, in group A there was no improvement in quality of life compared to the start of the study, nor was there an invariable difference in quality of life between A and B. In the file submitted, the company concluded that "[drug A] does not impair HRQoL and in some cases HRQoL improved relative to baseline." Because scores are not presented in the document for all points of the analysis, it is difficult to get a picture of the general trends revealed by the instruments used. Following a request for clarification from the Evidence Review Group (ERG), graphs are provided showing the evolution of the QoL measurements over time (see Fig. below). These graphs show that there is likely no significant difference between the two products in the change in quality of life from baseline (see figure on the right). Therefore, it is possible to agree with the conclusion that drug A does not alter QoL (relative to baseline), but there is no evidence that it leads to an invariable and lasting improvement in QoL. Without a transparent presentation of these outcomes, it is not possible to objectively assess the assumptions made in the economic evaluation, or to validate the modelled outcomes against the original outcomes of the study.



Box 5 – The PFS as a Surrogate Endpoint for Quality of Life?

In economic assessments, the impact on PFS is often interpreted as a benefit in terms of overall survival and quality of life. Unfortunately, evidence for this substitution is often lacking. A review by Hwang et al.[28] of the association between PFS and QoL in phase III clinical studies showed only a weak correlation (r = 0.34), regardless of the QoL domain examined. Such assumptions are therefore not evidence-based and can lead to very optimistic results of the economic evaluations.

The use of PFS as a surrogate endpoint for quality of life was justified in an economic evaluation as follows: symptoms associated with disease progression – which have a negative impact on QoL – are avoided as long as patients remain progression-free; staying progression-free delays the initiation of chemotherapy, which can be associated with high toxicity and lower QoL; chemotherapy leads to (sometimes great) anxiety in patients, which has a negative effect on QoL; patients whose disease does not progress are lively and able to work and maintain a certain 'normality' (family and social life). In addition, the diagnosis of metastatic cancer and subsequent treatment may also negatively affect caregivers, who are at increased risk of depression and loss of QoL compared to the general population.

All these arguments actually argue in favour of using tools that can measure these different effects, rather than using the PFS as a surrogate endpoint for the QoL. The EQ-5D may be a good candidate, as this questionnaire contains sections on daily activities, anxiety, and depression. There are also ways to measure the impact on absenteeism and attendance at work and on the quality of life of carers. Such instruments are certainly more reliable than making questionable assumptions about quality of life based on the PFS measurement.

6.2. Uncertainties with regard to MEAs

At the time of approval of a new drug, evidence of efficacy and cost-effectiveness is often still limited. To compensate for this disadvantage, public health authorities and pharmaceutical companies have established alternative funding mechanisms that allow for the sharing of risks associated with these uncertainties until more reliable data are available. This is to prevent patients' access to these potentially beneficial innovations from being delayed. These are the so-called "*Managed Entry Agreements*" (MEAs). They allow a pharmaceutical company to receive a reimbursement for a new product while continuing to collect the data needed to demonstrate its effectiveness and cost-effectiveness. On the basis of this information, the authorities can then make a more informed decision about reimbursement at a later stage.

The original idea, introduced in Belgium in 2010, made sense in itself, but these so-called "Article 81" agreements should remain exceptional. Today, however, we see that they have rather become the rule and the number of MEAs continues to increase year after year, at ever-increasing volumes and ever-higher prices. In addition, these agreements are confidential, which also creates problems for the pricing of other products, including generic products and biosimilars (see 6.2.3). Finally, these agreements are sometimes concluded despite negative advice from the Commission for the Reimbursement of Medicines (CRM) (in about half of these negative cases, according to the latest MORSE[p] report). In 86.2% of cases, the medicine is temporarily authorised within the framework of an MEA, even if no added value is claimed. It is clear that confidential contracts are therefore no longer reserved for medicines for which there are large unmet needs and potential high added value.

Most of these agreements (58%) currently relate to "antineoplastic and immunomodulatory agents", i.e. primarily cancer drugs.

[p] Monitoring of Reimbursement of Significant Expenses

6.2.1. *Refund mechanisms of the MEAs and taxes paid by the pharmaceutical industry*

In the introduction to this synthesis, we pointed out that the expenditure of the NIHDI for innovative oncological medicines in 2019 amounted to approximately one billion euros. This is an official figure based on the public prices of these drugs. In reality, this expenditure must be reduced by the amount of the discounts granted under the MEA agreements and the amount of the taxes, which constitute a reverse flow of money from the pharmaceutical industry to the NIHDI.

According to the MORSE report, it is not possible to make a detailed analysis of these cash flows due to the confidential nature of the various mechanisms involved. However, the MORSE report presents a general image. For the sake of completeness, the MORSE report also takes into account the revenues from the annual taxes paid by the pharmaceutical industry (see Table 3).

Table 3 – Evolution of gross expenditure for all medicines and net cost for the NIHDI (2014 - 2019) (in € 000)

	2014	2015	2016	2017	2018	2019
Gross expenditures medicines (1)	4,033,476	4,277,705	4,378,171	4,594,786	4,891,838	5,263,274
Refunds MEAs (2)	41,346	54,516	123,556	273,351	359,310	605,043
(3) = (1) min (2)	3,992,130	4,223,189	4,254,615	4,321,435	4,532,528	4,658,231
Taxes and clawback (4)	223,896	281,085	321,517	344,371	399,283	431,510
Net costs (5) = (3) min (4)	3,768,234	3,942,104	3,933,098	3,977,064	4,133,245	4,226,721

The MORSE report reports an increasing number of MEA applications, recording a sharp increase in gross expenditures of products for which an MEA was concluded, from approximately €225 million in 2014 to €653 million in 2016 and to nearly €1.6 billion in 2019. The amount of refunds related to these confidential contracts has also increased significantly over time, from approximately €41 million in 2014 to approximately €121 million in 2016 and to over €600 million in 2019. Expressed as a percentage, the magnitude of these refunds is also increasing: 38.5% in 2019 (€600 million in refunds compared to €1.6 billion under MEA).

In addition to the refunds under the MEAs, the pharmaceutical industry also pays a significant amount through other charges and taxes (see Table 3).

Combined, these refunds and charges amount to approximately €1 billion. Ultimately, we arrive at a net expenditure for all medicines of approximately €4.2 billion.

A document from Pharma.be points out that the increase in this net drug expenditure, taking into account the refunds via MEAs and taxes, is growing more slowly than the other NIHDI expenditure (+7.4% compared to +16% in the period 2012-2018). However, we note that the increase in spending is not the only important element; it primarily concerns the added value generated for the patient's benefit. And because there is a limited budget, it is important that the resources are invested where the added value is highest in comparison to expenditures.

6.2.2. *The industry is not encouraged to provide the missing evidence*

Compensation mechanisms such as MEAs are more aimed at speeding up reimbursement than at generating reliable scientific evidence. As we have seen, evidence of the clinical effectiveness of innovative oncology drugs is therefore becoming less and less well documented. One might even wonder whether current MEA practices have meant that this crucial information may never be generated, even after the medicines have received a reimbursement (even if temporary). After all, it is very difficult to cancel the reimbursement of a product once you are used to using it. The MEA agreements currently in use encourage requests for reimbursement based on immature data, but **do not provide incentives to subsequently generate reliable evidence** (see KCE report 288). That's why we thought about mechanisms to rectify this situation, without slowing down patients' access to innovations that are really relevant to them.

6.2.2.1. *Before Marketing Authorisation*

In both the United States and Europe, regulatory authorities are assessing the expected effects of new drugs and their benefit-risk balance, **and not their advantages and disadvantages compared to existing alternatives**.[19] Medicines thus often receive marketing authorisation based on studies that can be used by EMA for a benefit-risk analysis, but are not optimal for reimbursement decisions that are a national competence. It is also questionable whether studies based on surrogate endpoints provide optimal or even meaningful information for patients and clinicians.[19] As in our critique of the current application of the Belgian MEAs, Davis et al.[6] even question whether the current European regulatory framework and current research practices have not created a situation where critical information about outcomes that are most important to patients may never be generated once oncology drugs are approved for widespread use.

To solve this situation, Naci *et al*[19] proposed **five principles** for generating comparative scientific evidence for interventions before they obtain their marketing authorisation. A number of these principles presented in the box below are also explicitly addressed in our recommendations. The fifth principle is addressed to the national policy makers (payers) that the MEA system could be used for (see 6.2.2.2). The first four principles are intended for the European regulator (EMA). The main purpose of these principles is to make the studies not only useful for EMA for marketing authorisation, but also to provide better information that is useful to patients, physicians and policy-makers in reimbursement decisions. This should be taken into account from the beginning (i.e. from the studies to be designed for the marketing authorisation application) to ensure that **the study design includes suitable active control groups, relevant endpoints (particularly in terms of overall survival and quality of life) and provides adequate follow-up without undue crossover.** That way, the study can be used to **generate evidence needed to support reimbursement decisions**. This is an international objective that requires **cooperation between HTA agencies, the EMA and industry, in particular through early dialogues.**

Box 6 – Naci et al.'s[19] five principles for generating comparative scientific evidence before obtaining marketing authorisation

1. Patients and clinicians should be systematically informed about the existence or absence of comparative data on the new products;
2. regulators should be more selective in using mechanisms that allow drug (and medical device) approval based on incomplete data;
3. regulators should promote randomised studies with active comparators;
4. regulators should use prospectively designed network meta-analyses based on existing and future randomised trials;
5. payers should use their policy levers and negotiating power to encourage the generation of comparative evidence on new and existing medicines, for example, by explicitly considering proven added benefit in pricing and payment decisions.

6.2.2.2. After obtaining marketing authorisation

The other crucial phase where national policy-makers can influence the gathering of the necessary evidence is the phase where reimbursement decisions are made. However, the current use of MEAs in Belgium is far from optimal to support this capability. In a previous report (KCE report 288), the KCE has already noted that little evidence is effectively generated in the context of MEAs, and that the main uncertainties identified in the initial assessment of the Commission for the Reimbursement of Medicines (CRM) are often still present at the end of the contract. The current approach does not offer a solution to this problem. KCE's report refers to a number of elements:

- **Additional scientific data**: **if additional data are to be collected, this must be clearly stated in the contract. Otherwise, manufacturers will not be encouraged to provide reliable evidence**. This collection of additional data entails significant costs for the company and carries the risk that the new data obtained will not confirm the added value of the product (or even confirm that the product is less effective than the comparator). The KCE's analysis of the first 16 Belgian MEAs after they ended showed that no additional evidence had been generated to answer the research questions posed in the initial assessment (before the MEA).
- **Withdrawal of reimbursement:** Once a product is reimbursed under an MEA, it is very difficult to reverse the reimbursement, regardless of the (lack of) evidence. On the contrary, it often happens (in 56.48% of the cases according to the latest MORSE report) that after an MEA, the expired agreement is simply renewed. This reduces the incentive to actively gather the necessary evidence to address existing uncertainties. **Therefore, the consequences of not searching for the requested additional data should be indicated from the outset in order to encourage the companies to search for these data in a timely manner.** Since Belgium has very little bargaining power in this negotiation, it is necessary to consider whether the demand for additional scientific evidence can be pursued at national level or whether international cooperation is necessary.
- **Wrong MEA selection:** Ideally, the MEA type selected should be consistent with the uncertainty that the MEA is supposed to remove. In practice, there is a risk that purely financial MEAs will be concluded. Financial MEAs (e.g. refunding a percentage of turnover) are, after all, easier and cheaper for the company and the government than, for example, setting up a new RCT (in consultation). In addition, further monitoring should also be considered of existing RCTs (without undesired crossover) and/or performing meta-analyses, which is less financially demanding. In Belgium**, pharmaceutical companies are de facto free to choose how they collect data in the context of an MEA.** Waiting until the end of the contract is a waste of time if it can be determined from the outset that the proper efforts are not being made to collect the necessary evidence.

Cipriani et al formulated **seven principles** to encourage pharmaceutical companies (and companies manufacturing medical devices) to generate comparative data in the post-market period (see Box 7).[20] Several of these principles can be included in the MEAs in Belgium, starting from a clear description of the identified gaps and linking these gaps to the correct study design. For example, if only an RCT can answer the research questions, no proposals for observational studies should be accepted. The authorities may

even consider granting **the first reimbursement in the context of an RCT**, e.g. to avoid delays due to recruitment problems. For example, the intervention can only be reimbursed once a sufficient number of patients have been admitted and the study is ongoing. A new assessment will be performed once the results are available. Such an approach is already possible, but is rarely used. It is not necessarily much more expensive (and may even be cheaper than a regular reimbursement) and is scientifically and politically sound.

Box 7 – Cipriani et al.'s[20] seven principles for generating comparative scientific evidence after obtaining marketing authorisation

1. Regulators, HTA agencies and payers should develop customised evidence generation plans, ensuring that future post-approval studies address any limitations of the data available at the time of market entry;
2. Post-marketing studies should be designed hierarchically: priority should be given to efforts aimed at evaluating a product's net clinical benefit in randomised trials compared with current known effective therapy;
3. Post-marketing studies should include appropriate (active) comparators;
4. The use of non-randomised studies for the evaluation of clinical benefit in the post-marketing period should be limited to instances when the magnitude of effect is deemed to be large or when it is possible to reasonably infer the comparative benefits or risks in settings, in which doing a randomised trial is not feasible.
5. The efficiency of randomised trials should be improved by streamlining patient recruitment and data collection through innovative design elements.[q]
6. Governments should directly support and facilitate the production of comparative post-marketing data by investing in the development of collaborative research networks and data systems that reduce the complexity, cost, and waste of rigorous post-marketing research efforts.
7. Financial incentives and penalties should be developed or more actively reinforced.

However, a major problem remains, namely Belgium's **weak negotiating position**. This problem also occurs in other (smaller) countries. Therefore, **more international cooperation**, for example in the context of the BeNeLuxA, could represent a major step forward, for research questions that cannot be addressed at national level both in demanding additional evidence and in price negotiations.

6.2.3. Confidential pricing creates a lack of transparency with negative consequences

In the short term, confidential price cuts are expected to solve the overpricing problem and speed up patients' access to innovations. Some even claim that introducing MEAs will save money… However, these so-called savings should be viewed with caution. For example, what is the value of a discount of 10, 20 or even 50% if the final price paid is still much higher than the alternatives? Even more so, what if the product does not offer any real added value? Today it is clear that confidential price discounts do not encourage the establishment of acceptable market prices. The opposite is true, as companies know that confidential discounts will be negotiated in the MEAs and already factor this into their initial pricing. Presenting the larger refunds as a source of revenue for the government after much more money has been spent first has to be interpreted with some nuance.

[q] Cipriani *et al.* mention that RCTs can benefit from innovative methodological designs and refer to 'adaptive trials', 'basket trials', 'platform trials', 'registry-based trials', and 'umbrella trials'. For an overview of these different types and their strengths and weaknesses, please refer to the summary tables in the original study.[20]

Dr Ri De Ridder, former Director General of the Health Care Service of the NIHDI, pointed this out in his book, *Goed Ziek*: "The problem is that the negotiations on the price between the competent minister and the companies are done in complete secrecy and that no one has insight into the amounts the company is demanding. There is a total lack of transparency, no one knows the actual cost of developing the drug, and there are no independent audits evaluating these types of contracts."[29] With regard to this last point, we note that in 2020 the Parliamentary Committee on Public Health approved a draft law, based on which the Belgian Court of Auditors can check new confidential agreements. This law is a small step forward in terms of transparency, but only applies to future contracts. Moreover, the Court of Auditors has no medical or methodological competence, for example to assess applications for additional research. The select group of persons with insight into the contracts remains bound by confidentiality, and independent researchers are therefore still unable to conduct a neutral evaluation.

In addition, more and more medicines are reimbursed under MEAs in situations that were not originally intended, some of which do not even claim added value. How is that possible? If the current standard treatment, i.e. the comparator for the new product, is already covered by an MEA, then open negotiation is impossible and there is no other solution than to have the new product also covered by an MEA, regardless of its claimed added value. **As a result of the increasing use of MEAs, prices are thus not only not transparent for innovative medicines, but also for many comparators, the possible subsequent treatments, or even generic products and biosimilars.** This **snowball effect,** which contributes to the aforementioned uncontrollable increase in pharmaceutical expenditure reimbursed under MEAs, **gradually increases the non-transparency of the system**.

This situation leads to incorrect calculations of ICERs, as the latter can change greatly depending on the cost of both the intervention and the current standard of care or subsequent treatment. **The real cost-effectiveness of an intervention thus becomes entirely obscured,** both for external researchers and for the pharmaceutical company itself. They cannot make correct calculations when confidential discounts are applied to the comparator and/or subsequent treatments.

The system of confidential pricing as a whole therefore makes economic assessments considerably more complicated and unusable, and poses problems for any transparency or accountability of reimbursement decisions taken.

Conclusion: MEA agreements should have been exceptions, but in 2019 more than €1 billion[r] was spent on these secret contracts. As stated by Dr Ri De Ridder, "the article 81 agreements were intended as an exception… **Solutions for a relatively small group of patients thus put a lot of pressure on health insurance expenditure**."[29] It is now up to policy-makers to think about the future of these MEAs. In this report, we make a number of constructive proposals to make it **a system that not only seeks to resolve budgetary uncertainties, but also addresses the resolution of clinical uncertainties by supporting the generation of the necessary scientific evidence.**

[r] In 2019, gross expenses were approximately €1.6 billion, of which approximately €600 million was returned.

7. ADDITIONAL STATEMENTS THAT DESERVE THE NECESSARY NUANCE

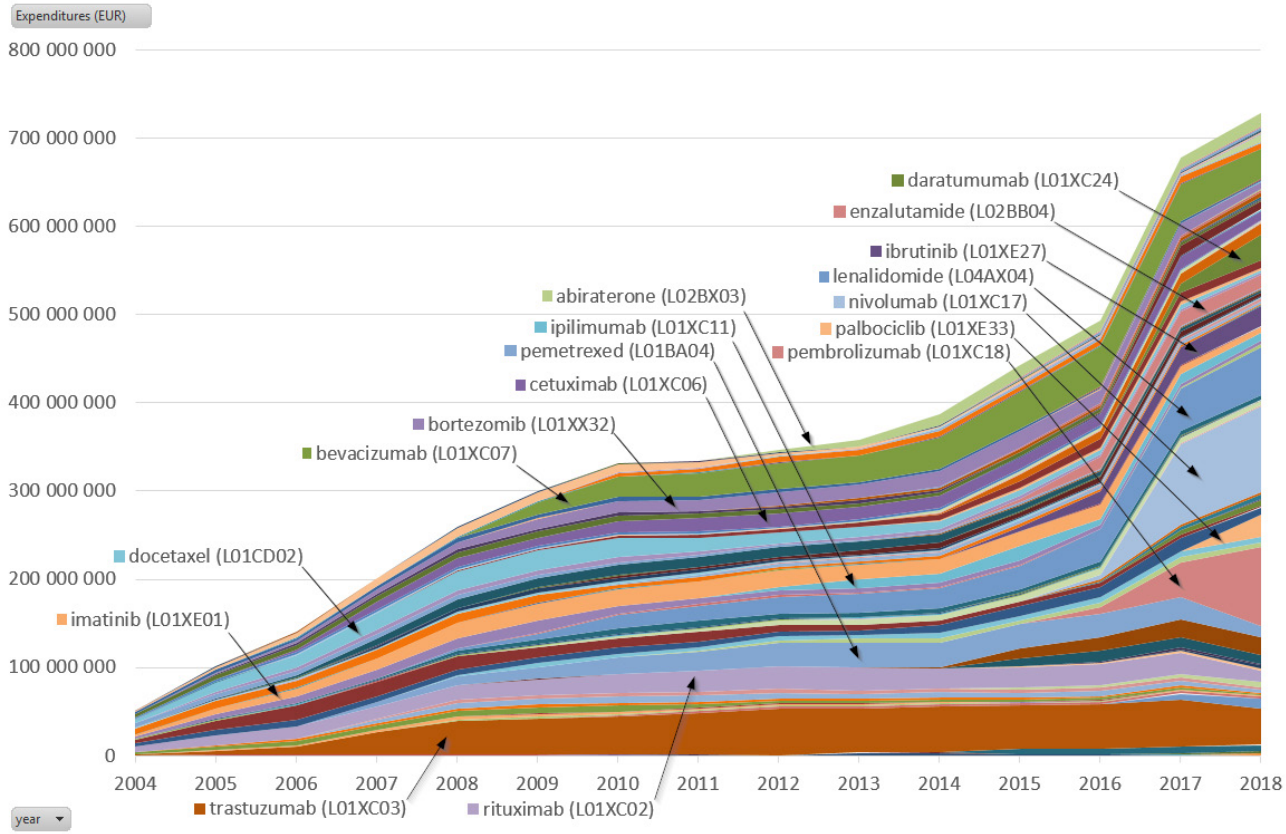
The debate here is very multifaceted, and many of the arguments put forward by the various stakeholders during discussions on this matter are beyond the scope of this report. We have therefore not gone into them in detail, but would like to briefly mention a few here, because they must be viewed with certain nuances.

Some argue that the relative increase in drug expenditure in recent years has been smaller than increases in other health care domains. Such comparisons of expenditure are always risky. First, data depend on what is included in the cost representation (e.g. all medicines or only those administered in a hospital) and on the reference years used. Figure 1 provides, for example, an overview of the expenditure per calendar year for all innovative medicines included in our research. However, this picture is not complete because only expenditure in the 5 years after diagnosis is included; moreover, the last two years are not yet complete and are therefore an underestimate of the expenditure.[s] On the other hand, because the discounts obtained in MEA contracts are confidential, it is also certain that the figures included are an overestimation.

Secondly, the comparison with other sectors can be misleading, especially when there is a chronic underfunding of certain sectors (e.g. mental health care) and a decision is made to catch up in terms of budgeting those sectors. Ultimately, the most critical argument for assessing the efficiency of spending is the added value created for the population.

[s] For clarification we refer to section 3.1.1.2 in the scientific report.

Figure 1 – Evolution in expenditure for oncological drugs included in this report (per calendar year: 2004-2018)



Note: for a description of the included medicines, we refer to section 3.1.1.2 of the scientific report.

Another frequent argument is that the high amounts paid for innovative medicines are reinvested in research and development. This engine of innovation also creates a large number of jobs in this sector. However, this claim does not take into account the fact that research is also largely funded by the public sector. Many of the spin-offs resulting from this government-funded research at our universities are being bought up by industry in the final stages of new product development and are clearly lucrative investments for commercial pharmaceutical companies. If health insurance has to pay a high price for these products, society is actually paying twice. US researchers have attempted to determine to what extent the later stages of new drug development – leading to the securing of intellectual property rights – were initially based on government investment.[30] Based on their analysis of patents for new drugs approved between 2008 and 2017 by the FDA, they conclude that "publicly supported research had a major role in the late stage development of at least one in four new drugs, either through direct funding of late stage research or through spin-off companies created from public sector research institutions." The requisite nuance is also needed here.

Of course, the costs for all research that does not lead to the marketing of a medicine must also be taken into account. However, those costs are generally not very transparent and should be largely offset by the very generous profit margins that can be levied on patented products. At the end of 2017, revenue from the sale of 99 FDA-approved cancer drugs between 1989 and 2017 were 14.5 times greater than the industry's investment in research and development. We can therefore ask whether these profit margins do not encourage the pharmaceutical industry too much to invest substantially, perhaps even disproportionately, in the development of products in this oncology sector at the expense of research into other pathologies.

In any case, the market for cancer drugs is not a traditional market: the presence of monopolies via patents and a third-party payer system whereby the patient and the doctor naturally want the best treatment (which is of course an ideal combination to charge high prices); the policy-maker who is put under heavy pressure by the media when they make unpopular decisions such as refusing a reimbursement if the added value is uncertain or too small in relation to the requested price; a system where official list prices continue to rise but do not always reflect what is actually being paid nor reflect the true underlying costs; sustained obscure pricing information where companies know what they are paying in different countries but the countries don't have a view on this (and everyone is told they are receiving the best price); the lack of international cooperation, something which is increasingly demanded but not easy to achieve, etc.

However, health authorities also have to deal with other points of view, from the "recipients" of care themselves, namely the patients and doctors. They want to be able to use the best treatments as quickly as possible. Even a limited or uncertain added value can be considered sufficient when patients and doctors are confronted with a serious or hopeless situation. These choices are therefore often particularly difficult for policy-makers. However, making choices for an entire population is quite different from making choices for an individual patient. The payer's stance – to spend the available resources 'as effectively as possible' – is often much harder to defend than that of patients, especially when the media gets involved. The patient's expectations also do not always reflect reality. In a study of 134 patients with metastatic cancer who had already received 6 months of chemotherapy (median duration), 88% said they were ready to start a new treatment. However, when asked to specify the minimal survival gain needed to make this decision, they said they expected 18 months (median threshold, except in the case of colorectal cancer, where it was 36 months).[31] This hope and expectation far exceed the actual survival gain offered by the vast majority of new cancer drugs. Therefore, it is not only necessary to generate reliable evidence of the added value of innovative oncology drugs in terms of survival and/or quality of life to enable correct reimbursement decisions, but also to inform doctors and patients objectively. These different points of view should be part of a broad public debate.

8. CONCLUSION

The findings in the literature and this study reinforce each other. Evaluations of EMA and FDA dossiers point to major uncertainties about the added value of innovative cancer drugs when they receive their marketing authorisation. The studies also indicate that many of these uncertainties are not answered after several years, or that the added value is often limited in reality. Our observational Belgian data show that substantial improvements in survival have often not been observed in the last 15 years for many of the 12 studied indications, while new drugs with increased expenditure have been introduced. There are also the cited shortcomings in measuring and identifying the impact on quality of life, the (too) great confidence in surrogate endpoints, etc. These uncertainties about the added value of innovative medicines are also combined with secret contracts about their price that makes the system completely non-transparent.

It is now up to the European and (inter)national governments to seriously question this system and to decide how they want to use it in the future. In the first place, we recommend that it evolves into a system that tries to resolve clinical uncertainties and clearly map out the real added value for the patient of new interventions compared to existing treatments. This is an essential objective if policy-makers, doctors and patients are to be well informed and able to make decisions on a reliable basis. The findings in this study based on the (recent) past can help policy-makers improve policy in the future. We would like to refer to our recommendations, which are aimed at European and (inter)national governments, doctors and patients.

RECOMMENDATIONS[t]

To the European Commission, the European Medicines Agency (EMA) & the NIHDI:

1. **We recommend not focusing primarily on early access to "innovative" oncology drugs. The primary concern should be to provide timely access to medicines for which clear and reliable added value for the patient has been demonstrated. Below we give concrete recommendations to achieve this goal.**

To the European Commission, EMA & companies:

2. **We recommend conducting studies already in the pre-marketing phase that are suitable for registration purposes, reimbursement decisions and support for physicians and patients when taking decisions about treatments. Since it is more difficult to provide additional evidence of effectiveness after marketing authorisation was granted, it is crucial to start the necessary studies in a timely manner.**
3. **In designing these studies, we recommend that there is more focus on including the correct (active) comparator(s), relevant endpoints (including overall survival and quality of life) and adequate follow-up without inappropriate crossover of patients.**
    - **A close collaboration of HTA agencies/payers with the support of EMA for this approach to start up practice-relevant studies in the pre-marketing phase must be legally anchored in European law (see recommendation 5).**
    - **Given the often uncertain and limited added value of cancer drugs, randomised studies must be prioritised as the most reliable source for estimating the added value of new interventions. Non-randomised observational data should not simply be regarded as a reliable study design for estimating the treatment effect.**
    - **These randomised trials should pay due attention to the following:**
        - **Including a population that reflects the future target population.**
        - **Incorporating the standard treatment as a comparator. Elements of treatment optimisation (e.g. the duration of the treatment) should also already be evaluated in the pre-marketing phase.**

[t] Only KCE is responsible for the recommendations.

- **Relevant endpoints are quality of life and survival. These should be included in the studies where possible.**
- **Surrogate endpoints can only be useful where they are sufficiently scientifically validated for the specific condition and mechanism of action of the drug. We recommend following the EUnetHTA guideline whereby data on overall survival as well as quality of life should be systematically collected in the metastatic setting (stage IV).**
- **Measuring quality of life, using both disease-specific and generic utility tools (as also recommended by EUnetHTA). Quality of life should also be measured throughout the full follow-up of the study (e.g. also after disease progression).**
- **Strictly avoiding inappropriate crossover of patients in the study.**

4. **We recommend strict monitoring regarding the timely and complete reporting of all study results. For example, the impact on quality of life must be reported transparently (i.e. results for all treatment arms and all time points when this outcome was measured). The full results of clinical studies should be made public and never be confidential. Like other key endpoints, quality of life and overall survival should be included in the EPAR (European Public Assessment Report).**

To the Minister of Public Health and the European Commission, regarding EMA:

5. **We recommend that the European Commission adjust the regulatory framework for the EMA, while respecting the difference in competences between the EMA and the national authorities. It should be enshrined that through mandatory early dialogues, the input of the payers and HTA bodies in the member states is taken into account when drafting the protocol of the confirmatory clinical trials. This will help to prevent the studies designed from not providing the information needed to support subsequent reimbursement decisions (see also recommendations 2 and 3).**
6. **We recommend the European Commission urging the EMA to make more selective use of conditional marketing authorisation if evidence as to the treatment's effect is insufficient. This approval must then be made conditional, with an explicit requirement to collect the required data within a certain period. Conditional approval should be automatically withdrawn if the necessary studies are not initiated/continued/delivered. This should be sufficient incentive to deliver the required data on time. It should be further investigated which criteria can be used for the selective application of the conditional market authorisation and how compliance with the conditions imposed can be monitored.**

To the NIHDI:

7. **When reviewing each submitted dossier, we recommend checking that all study results are present (for all studies initiated and for all endpoints incl. quality of life) when reviewing each file.**
8. **We recommend only accepting the use of surrogate endpoints where they are sufficiently scientifically validated.**
9. **We recommend using the system of managed entry agreements (MEAs) more selectively and ensuring the necessary data are actually collected. We recommend striving more for an evidence generation system that also helps to resolve the clinical uncertainties. The moment of the reimbursement decision can be used as leverage to achieve this. To make this run efficiently, we recommend the following:**
    a. **We emphasize that the uncertainties should initially be addressed at European level (see recommendations regarding EMA). Where there is still a major residual uncertainty, it can be determined at a national level which type of study is necessary to answer the outstanding research questions. International cooperation is recommended for this (e.g. in the context of the BeNeLuxA initiative).**
    b. **We recommend paying attention to the correct study design for collecting further information in order to answer the original research questions. When using observational data from registers, they must be critically examined whether the available data will be able to provide an answer to the open research question. While registry-based RCTs can be a reliable source for identifying treatment effect, this is questionable with non-randomised registry information. We refer again to other requirements for further research (see recommendations regarding EMA).**
    c. **This question about the correct study design must be asked when concluding the agreement and must be part of this agreement. Failure to start/continue/complete the study on time should automatically lead to termination of the agreement in order to provide the necessary incentives to carry out this study on time.**
    d. **In order to make randomised research possible in practice, a restriction on the reimbursement to study patients can be considered in a first phase. An intervention by the payer to execute this study can be considered exceptionally (and put into perspective with the expenditure if the intervention were to be reimbursed without any**

other condition). This does not alter the fact that the companies must make every effort to start the necessary studies before marketing authorisation is granted.

10. Given the lack of transparency and unsustainability of the current confidential price system, we recommend working with other countries to move towards a system with more transparent and acceptable public prices, which would eliminate/reduce the need for confidential agreements with artificially high public prices. An exception to the confidential prices could be that a lower price is agreed in anticipation of more reliable and relevant study results.
11. We recommend making all the assessment files of all reimbursement applications public (including those from before 2019). No results of clinical studies should be treated as confidential.

To the BCR & NIHDI:

12. We recommend requesting permission to have permanent access to reimbursement data for a longer period (>5 years), possibly until the patient's death.
13. We recommend making it possible to collect more refined data on, among others, sub-populations based on biomarkers (e.g. HER2 overexpression in breast cancer). This can be done by automatically forwarding the test results from the lab systems or by optimising the use of innovative techniques such as Natural Language Processing. It may also be useful to collect biomarker data in view of a relevant historical control group in the rare cases where a randomised trial is really not possible, especially in very small sub-populations.
14. We also recommend systematically collecting data on progression and relapse.

To all parties involved in clinical research, including the Medical Ethics Committees:

15. We recommend that due consideration be given in every clinical trial to the measurement and timely and complete reporting of quality of life (see also EUnetHTA guidelines in recommendation 3).

To physicians, nurses, patients, patient representatives and independent research institutions:

16. **We recommend supporting the demand for more reliable and relevant information about the added value of cancer drugs and demanding data that are important for clinical decisions (such as longevity and quality of life).**
17. **All parties must be aware that rapid access to innovative medicines only makes sense if there is clear added value for the patient. Rapid access without (generating) sufficient evidence of the drug's added value is detrimental to all parties.**
18. **The industry, physicians and patients must be aware that reimbursement of a contracted product is temporary and may be discontinued, especially if there are uncertainties about clinical efficacy.**

To all actors in society, including patient representatives, healthcare providers, industry, policy makers, the general public, etc.:

19. **A public debate is desirable on various aspects of the reimbursement of medicines, such as identifying the added value of innovative medicines, (rapid) access, affordability, etc.**

REFERENCES

1. Directie Farmaceutisch Beleid – Dienst voor Geneeskundige Verzorging (RIZIV). Monitoring Of Reimbursement Significant Expenses MORSE - Rapport 2020 (gegevens 2019). RIZIV - Rijksinstituut voor ziekte- en invaliditeitsverzekering; 2020.
2. Inovigate. Oncology budget challenge initiative: Multi-stakeholder recommendations for oncology therapeutics budget sustainability. Summary of Round Table 1, held on November 7th, 2019 at RIZIV/INAMI. 2019.
3. Kantarjian HM, Fojo T, Mathisen M, Zwelling LA. Cancer drugs in the United States: Justum Pretium--the just price. J Clin Oncol. 2013;31(28):3600-4.
4. OECD. Pharmaceutical Innovation and Access to Medicines - Executive Summary. Organisation for Economic Co-operation and Development (OECD); 2018.
5. Naci H, Carter AW, Mossialos E. Why the drug development pipeline is not delivering better medicines. BMJ. 2015;351:h5542.
6. Davis C, Naci H, Gurpinar E, Poplavska E, Pinto A, Aggarwal A. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. BMJ. 2017;359:j4530.
7. Grossmann N, Robausch M, Rosian K, Wild C, Simon J. Monitoring evidence on overall survival benefits of anticancer drugs approved by the European Medicines Agency between 2009 and 2015. Eur J Cancer. 2019;110:1-7.
8. Commission de la protection de la vie privée. Beraadslaging nr 09/071 van 15 september 2009, laatst gewijzigd op 18 februari 2014, met betrekking tot de mededeling van persoonsgegevens door de verzekeringsinstellingen aan de Stichting Kankerregister in het kader van artikel 45 quinquies van het KB nr. 78 van 10 november 1967 betreffende de uitoefening van de gezondheidsberoepen / Délibération n°09/071 du 15 septembre 2009, modifiée le 18 février 2014, relative à la communication de données à caractère personnel par les organismes assureurs à la

Fondation Registre du Cancer dans le cadre de l'article 45quinquies de l'AR n° 78 du 10 novembre 1967 relatif è l'exercice des professions des soins de santé. [Web page].2014. Available from: https://www.privacycommission.be/sites/privacycommission/files/documents/d%C3%A9lib%C3%A9ration_SS_071_2009.pdf

9. Wise P. Cancer drugs, survival, and ethics. BMJ. 2016;355(i5792).
10. NICE TA569. Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer. NICE, National Institute for Health and Care Excellence; 2019.
11. Banerjee R, Prasad V. Are Observational, Real-World Studies Suitable to Make Cancer Treatment Recommendations? JAMA Netw Open. 2020;3(7):e2012119.
12. Kumar A, Guss ZD, Courtney PT, Nalawade V, Sheridan P, Sarkar RR, et al. Evaluation of the Use of Cancer Registry Data for Comparative Effectiveness Research. JAMA Netw Open. 2020;3(7):e2011985.
13. Gyawali B, de Vries EGE, Dafni U, Amaral T, Barriuso J, Bogaerts J, et al. Biases in study design, implementation, and data analysis that distort the appraisal of clinical benefit and ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) scoring. ESMO Open. 2021;6(3):100117.
14. Haslam A, Prasad V. When is crossover desirable in cancer drug trials and when is it problematic? Ann Oncol. 2018;29(5):1079-81.
15. Hilal T, Gonzalez-Velez M, Prasad V. Limitations in Clinical Trials Leading to Anticancer Drug Approvals by the US Food and Drug Administration. JAMA Intern Med. 2020;180(8):1108-15.
16. Prasad V, Grady C. The misguided ethics of crossover trials. Contemp Clin Trials. 2014;37(2):167-9.
17. European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.5). 2017. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guidelineevaluation-anticancer-medicinal-products-man-revision-5_en.pdf
18. Food and Drug Administration. Clinical trial endpoints for the approval of cancer drugs and biologics guidance for industry. 2019. Available from: https://www.fda.gov/media/71195/download
19. Naci H, Salcher-Konrad M, Kesselheim AS, Wieseler B, Rochaix L, Redberg RF, et al. Generating comparative evidence on new drugs and devices before approval. Lancet. 2020;395(10228):986-97.
20. Cipriani A, Ioannidis JPA, Rothwell PM, Glasziou P, Li T, Hernandez AF, et al. Generating comparative evidence on new drugs and devices after approval. Lancet. 2020;395(10228):998-1010.
21. EUnetHTA. Guideline - Endpoints used in Relative Effectiveness Assessment: Surrogate Endpoints. 2015.
22. Ciani O, Davis S, Tappenden P, Garside R, Stein K, Cantrell A, et al. Validation of surrogate endpoints in advanced solid tumors: systematic review of statistical methods, results, and implications for policy makers. Int J Technol Assess Health Care. 2014;30(3):312-24.
23. Prasad V, Kim C, Burotto M, Vandross A. The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-analyses. JAMA Intern Med. 2015;175(8):1389-98.
24. Gyawali B, Hey SP, Kesselheim AS. Evaluating the evidence behind the surrogate measures included in the FDA's table of surrogate endpoints as supporting approval of cancer drugs. EClinicalMedicine. 2020;21:100332.
25. Belin L, Tan A, De Rycke Y, Dechartres A. Progression-free survival as a surrogate for overall survival in oncology trials: a methodological systematic review. Br J Cancer. 2020;122(11):1707-14.
26. Buyse M, Molenberghs G, Paoletti X, Oba K, Alonso A, Van der Elst W, et al. Statistical evaluation of surrogate endpoints with examples from cancer clinical trials. Biom J. 2016;58(1):104-32.
27. EUnetHTA JA3WP6B2-5 Authoring Team. Practical considerations when critically assessing economic evaluations. Guidance document. Diemen (The Netherlands): EUnetHTA; 2020.

28. Hwang TJ, Gyawali B. Association between progression-free survival and patients' quality of life in cancer clinical trials. Int J Cancer. 2019;144(7):1746-51.

29. De Ridder R. Goed ziek - hoe we onze gezondheidszorg veel beter kunnen maken. Halewyck V, editor.; 2019.

30. Nayak RK, Avorn J, Kesselheim AS. Public sector financial support for late stage discovery of new drugs in the United States: cohort study. BMJ. 2019;367:l5766.

31. Mende M, Trautmann K, Rentsch A, Hornemann B, Schuler US, Ehninger G, et al. Patients' perspectives on palliative chemotherapy of colorectal and non--colorectal cancer: a prospective study in a chemotherapy- experienced population. BMC Cancer. 2013;13:66.

COLOPHON

Title:	Do innovative medicines against cancer always have a real added value? – Synthesis
Authors:	Mattias Neyt (KCE), Carl Devos (KCE), Nancy Thiry (KCE), Geert Silversmit (BCR), Cindy De Gendt (BCR), Nancy Van Damme (BCR), Diego Castanares - Zapatero (KCE), Nicolas Fairon (KCE), Frank Hulstaert (KCE), Leen Verleye (KCE)
Project facilitator:	Els Van Bruystegem (KCE)
External experts:	Yves Beguin (CHU Liege), Thierry Berghmans (Institut Bordet), Martine Berliere (UCL – Université catholique de Louvain), Benoit Beuselinck (UZ Leuven), Paul Clement (UZ Leuven), Veronique Del Marmol (Hôpital Erasme), Hannelore Denys (UZ Gent), Alain Hendlisz (Institut Bordet), Ann Janssens (UZ Leuven), Patrick Neven (UZ Leuven), Bart Neyns (UZ Brussel), Fritz Offner (UZ Gent), Jean-Pascal Pascal Machiels (UCL), Emmanuel Seront (UCL), Jan Van Meerbeeck (UZ Antwerpen)
Stakeholders:	Kristel De Gauquier (Pharma.be), Bernard Debbaut (Christelijke mutualiteit), Christel Fontaine (BSMO Belgian Society of Medical Oncology), Julie Gusman (Pharma.be), Anne Hendrickx (Socialistische mutualiteit), Michail Ignatiadis (BSMO Belgian Society of Medical Oncology), Caroline Lebbe (Christelijke mutualiteit), Marc Peeters (College voor Oncologie), Ward Rommel (Kom op tegen kanker), Marc Van de Casteele (RIZIV – INAMI - Rijksinstituut voor ziekte- en invaliditeitsverzekering – Institut national d'assurance maladie-invalidité), Martine Van Hecke (Testaankoop), Chris Van Hul (Onafhankelijke ziekenfondsen), Johan Vanoverloop (IMA – AIM - InterMutualistisch Agentschap – Agence InterMutualiste), Anouk Waeytens (RIZIV – INAMI), Marjan Willaert (Pharma.be)
External validators:	Elizabeth Eisenhauer (Queen's University at Kingston, Oncology Department), (Beate Wieseler (Head of IQWiG's drug assessment department), Philippe Van Wilder (Ecole de Santé Publique - Université Libre de Bruxelle)s
Acknowledgements:	Inneke Van De Vijver (RIZIV – INAMI), Anouck Waeytens (RIZIV – INAMI), Stephan Devriese (KCE)
Reported interests:	'All experts and stakeholders consulted within this report were selected because of their involvement in the topic of innovative oncology. Therefore, by definition, each of them might have a certain degree of conflict of interest to the main topic of this report' Membership of a stakeholder group on which the results of this report could have an impact: Caroline Lebbe (CTG) Owner of subscribed capital, options, shares or other financial instruments: Johan Vanoverloop (Equity fund) Holder of intellectual property (patent, product developer, copyrights, trademarks, etc.): Michail Ignatiadis (ULB patent for CDK46 inhibitors) Fees or other compensation for writing a publication or participating in its development: Michail Ignatiadis (Novartis, Seattle Genetics), Bart Neyns (Co-author of publications to studies sponsored by Roche, Novartis, BMS, MSD),

	Philippe Van Wilder (Publication on the pharmaco-economic approach of vaccines. sponsored by the company pfizer belgium. Fee for writing meeting minutes and article writing) Participation in scientific or experimental research as an initiator, principal investigator or researcher: Michail Ignatiadis (Studies with Pfizer, Roche, Natera Inc), Jan Van Meerbeeck (Researcher in the international multicentre clinical studies leading to registration of pembrolizumab (Merck / MSD)), Philippe Van Wilder (Main author of a project for the economic evaluation of polyvalent immunoglobulins in the indication of CVID: project sponsored by the association PPTA) A grant, fees or funds for a member of staff or another form of compensation for the execution of research described above: Bart Neyns (Principal investigator clinical research from Pfizer and Novartis) Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Véronique Del Marmol (Consultancy for participation at national boards of Roche- BMS-Merck- Sanofi), Bart Neyns (Participation to the advisory board for BMS, MSD, Novartis, Amgen, Pfizer), Jan Van Meerbeeck (Advisory board for BMS and Pfizer Belgium), Philippe Van Wilder (Partner in the private consultancy firm SMART & BI. the company carries out health technology assessments within the framework of drug reimbursement, at the request of pharmaceutical companies or the public authorities) Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Michail Ignatiadis (Novartis, Amgen), Bart Neyns (BMS, MSD, Novartis, Amgen, Pfizer)), Jan Van Meerbeeck (Travel support to ASCO 2019 by BMS Belgium) Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Ward Rommel (President Task Force Access to Medicine ECL) Other possible interests that could lead to a potential or actual conflict of interest: Elizabeth Eisenhauer (Member of data safety monitoring committee for two trials utilizing PARP inhibitors), Caroline Lebbe (Representative CM in commission reimbursement of medicines and WG art 81.)
Layout:	Ine Verhulst
Disclaimer:	• **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** • **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** • **Finally, this report has been approved by common assent by the Executive Board.** • **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

Publication date:	05 July 2021
Domain:	Health Technology Assessment (HTA)
MeSH:	Antineoplastic Agents; Therapies, Investigational; Technology, High-Cost; Observational Study; Systematic Review; Randomized Controlled Trial; Neoplasms; Technology Assessment, Biomedical
NLM Classification:	QV 269
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2021/10.273/22
ISSN:	2466-6459

How to refer to this document?

Neyt M, Devos C, Thiry N, Silversmit G, De Gendt C, Van Damme N, Castanares-Zapatero D, Fairon N, Hulstaert F, Verleye L. Do innovative medicines against cancer always have a real added value? - Synthesis. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2021. KCE Reports 343Cs. D/2021/10.273/22.

This document is available on the website of the Belgian Health Care Knowledge Centre.